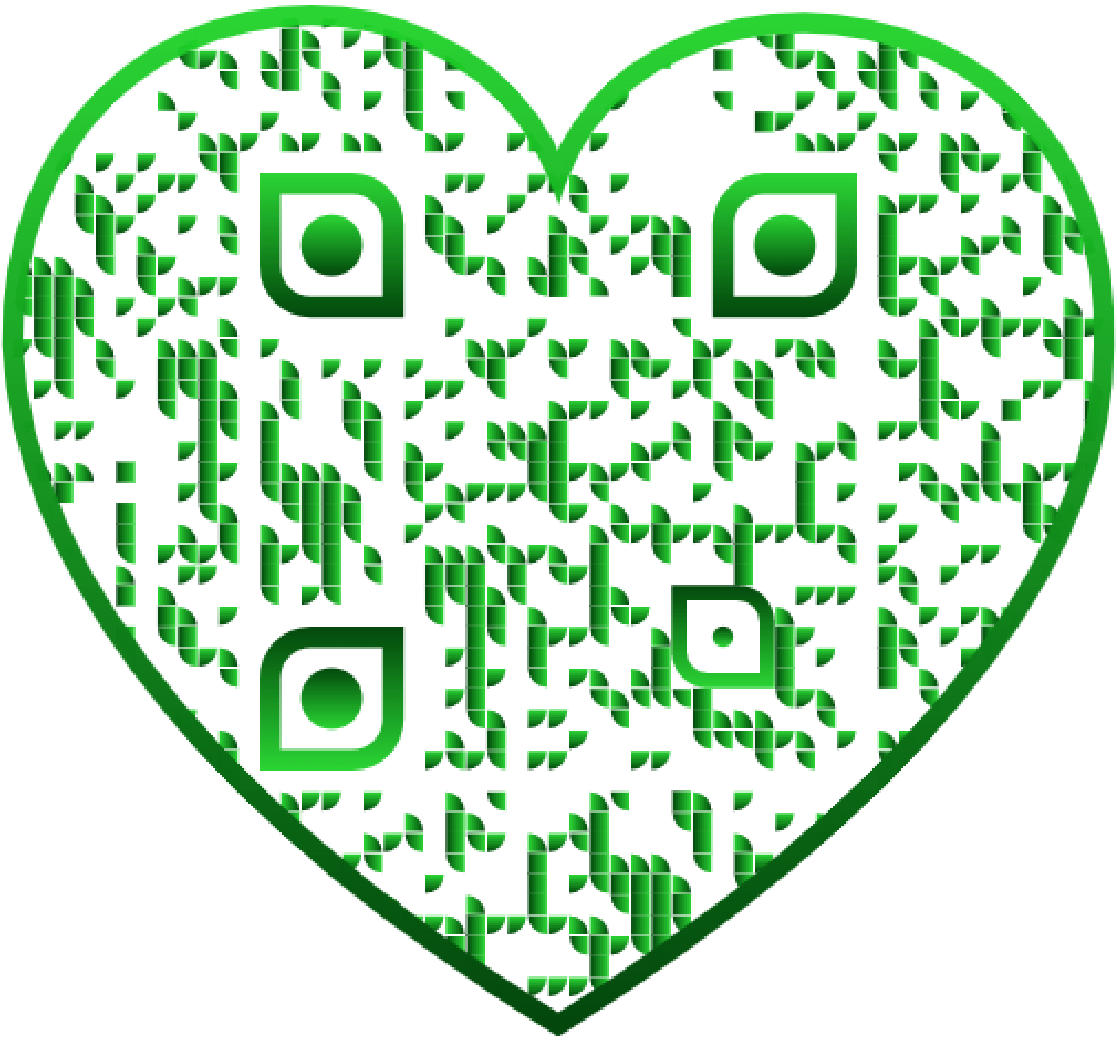
Lecture Notes

PHARMACOLOGY

Volume 1

- General
- Autonomic
- Autacoids

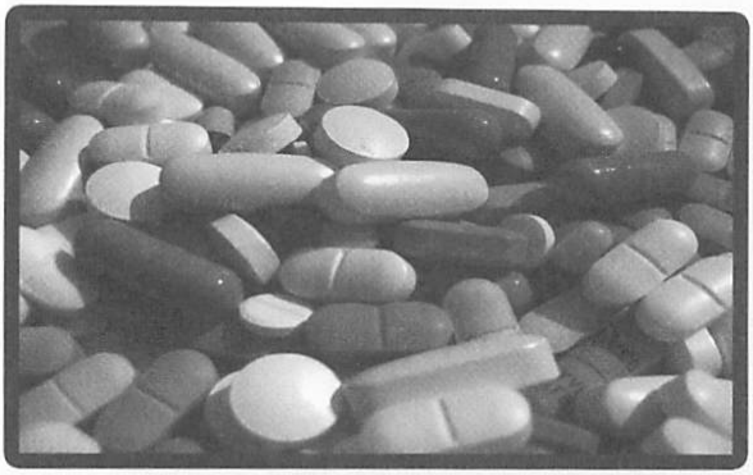
Pharmacology Department
Faculty of Medicine
Ain Shams University
2019/2020



Lecture Notes
PHARMACOLOGY

Volume 1

- General
- Autonomic
- Autacoids



Pharmacology Department
Faculty of Medicine
Ain Shams University
2019/2020

Preface

Pharmacology is an ever-changing medical science. The recent, rapid advances in molecular biology and biotechnology have added relevant information to drug therapy. This edition of "Lecture Notes on Pharmacology" provides the most recent advances in drug therapy within a concise framework.

This work is the result of the combined effort of the Professors of Pharmacology Department; Ain Shams University. "Each of us is unique in their own way. We have something to learn from everyone". Colleagues and students are encouraged to communicate their suggestions. Authors will be pleased to receive comments concerning this edition

Head of Pharmacology Department

Professor Dr. Lobna Bassyouni

2019-2020

Professors of Pharmacology Department

Head of Department

Prof. Dr. Lobna Bassyouni

Prof. Dr. Ahmed Nour Eldin
Prof. Dr. Sahar Kamal

Editorial Board: Prof. Dr. Ahmed Abdel-Salam - Prof. Dr. Olfat Hassan

Authors

Prof. Dr. Zeinab Labib
Prof. Dr. Ahmed Abdel-Salam
Prof. Dr. Olfat Hassan

Prof. Dr. Hoda Sallam
Prof. Dr. Mona Hassan
Prof. Dr. Dr. Sonia Saleeb
Prof. Dr. Osama El Serafy
Prof. Dr. Ahmed Khalil
Prof. Dr. Mohamed Abdel-Bary
Prof. Dr. Ahmed Abedel Tawab
Prof. Dr. Sawsan Abou el Fetouh
Prof. Dr. May Hamza
Ass Prof. Amany Helmy

Deep appreciation for the valuable contribution of

Prof. Dr. Yousria Wahba
Prof. Dr. Samira Mahmoud
Prof. Dr. Adel el Bakry
Prof. Dr. Mahdy Salama
Prof. Dr Sayed Kamel
Prof. Dr. Somia Massoud
Prof. Dr Atef EL-Esawy.
Prof. Dr. Ahmed Badawy

Computer graphics & designs: Dr. Essam Ghazaly - Dr. Mohamed Bahr

CONTENTS

1. General pharmacology....................................1 - 44

2. Adrenergic Pharmacology..................... 45 - 71

3. Cholinergic Pharmacology..................... 72 - 89

4. Autacoids Pharmacology ....90 - 105

General Pharmacology

Intended Learning Outcomes (ILOs)

Pharmacodynamics: By the end of this chapter, the student should be able to:

- Define basic terms in pharmacology: e.g., pharmacodynamics, pharmacokinetics bioavailability, first-pass effect, tolerance, intolerance, side effect, hypersensitivity idiosyncrasy, pharmacogenetics, mutagenicity, carcinogenicity, teratogenesis, iatrogenic disease, drug abuse.
- Describe the major animal & clinical studies carried out in clinical development.
- Describe the different signaling mechanisms for drug receptor interaction.
- Compare efficacy & potency of 2 drugs on the basis of their dose response curves.
- Predict efficacy of a partial agonist in presence & in absence of a pure agonist.
- Specify the types of antagonists used in pharmacology based on their effects on the dose response curves of their agonists.
- Describe 2 mechanisms of receptor regulation.

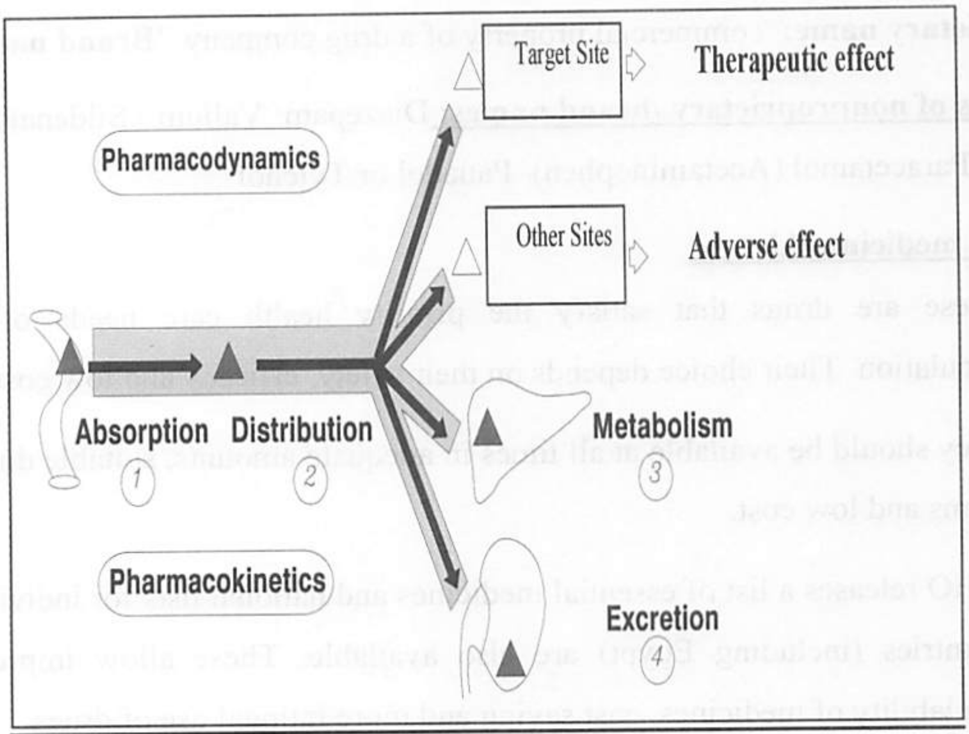
Pharmacokinetics: By the end of this chapter, the student should be able to:

- Realize the clinical importance of pka of a drug & pH of medium, in drug ionization, lipid solubility & subsequent absorption or excretion.
- List the major phase 1 & phase 2 metabolic reactions.
- List drugs with enzyme inducing or inhibiting properties giving examples of subsequent clinically important drug interactions.
- Calculate the half-life of a drug based on its clearance & volume of distribution.
- Calculate the loading & maintenance dosage regimen for oral or intravenous administration of a drug when provided with minimum therapeutic concentration, bioavailability, clearance& volume of distribution.
- Explain why drugs with saturation kinetics exhibit increased risk of toxicity.
- Calculate the dosage adjustment required for a patient with renal impairment.
- List important mechanisms of drug interactions and their clinical significance.

GENERAL PHARMACOLOGY

Pharmacology (Greek: pharmacon= drug, logos= discource in)

- It is the science that deals with drugs, their nature, pharmacodynamics, pharmacokinetics, therapeutic uses, preparations and administration.
- The 2 main divisions of pharmacology are pharmacodynamics and pharmacokinetics.


Target Site
Therapeutic effect
Pharmacodynamics
Other Sites
Adverse effect
Absorption
1
Distribution
2
Metabolism
3
Pharmacokinetics
Excretion
4

Fate of the drug in the body

Pharmacodynamics (Greek: dynamics= power)

- What the drug does to the organism. This includes the biological and therapeutic effects of drugs and their mechanism of action.

Pharmacokinetics (Greek: kinesis= movement)

- What the body does to the drug. This refers to the movement and alterations of the drug by the body. It includes Absorption, Distribution, Metabolism and Excretion of drugs (ADME) and their mathematical relationship.

Drug (French: drug= dry herb)

- It is a chemical substance that alters body functions and can be used for diagnosis, prevention or treatment of disease and is recognized in a pharmacopeia.

Drug Nomenclature

1. **Chemical name:** it describes the drug chemically but is not suitable for use in prescribing. The drug may be given a code name (e.g., RO-15-1788) for simplicity before the approved name is coined.
2. **Nonproprietary:** official or approved name.
3. **Proprietary name:** commercial property of a drug company **"Brand name"**

Examples of nonproprietary /brand names: Diazepam/ Valium - Sildenafil/ Viagra, - Paracetamol (Acetaminophen)/ Panadol or Tylenol

Essential medicines (drugs)

- These are drugs that satisfy the priority health care needs of the population. Their choice depends on their safety, efficacy and low cost.
- They should be available at all times in adequate amounts, suitable dosage forms and low cost.
- WHO releases a list of essential medicines and national lists for individual countries (including Egypt) are also available. These allow improved availability of medicines, cost saving and more rational use of drugs.

Examples of essential drugs: aspirin, paracetamol, warfarin

Orphan drugs

- These are drugs or biological products for diagnosis/ treatment/prevention of a rare disease or condition, or a common disease endemic only in poor countries for which the cost of developing and marketing is not expected to be recovered from the sales of that drug.
- Governments offer drug companies incentives e.g. tax benefits for development of orphan drugs.

EVALUATION OF NEW DRUGS

I. Evaluation in Animals

- It is conducted on experimental animals (at least 2 species, one of which is rodents):

  A. Safety Tests which include:

  - Acute, subacute and chronic toxicity studies.
  - Effects on reproductive function.
  - Carcinogenic and mutagenic potential.
  - Addiction liability.

  B. Pharmacologic Profile

  - It includes studying the effects of drugs on different body systems: CNS, GIT, CVS ...

II. Evaluation in Humans

- Begun after acute & subacute animal toxicity studies have been completed:

A. Phase I

- Done on small number of healthy volunteers.
- Trials are non-blind; both investigator & subject know what is being given.
- Compares human to animal responses & determines the clinical dose range.
- Pharmacokinetic measurements are often done in phase I.

B. Phase II

- Done on small number of patients to determine safety and efficacy.
- A single-blind design is often used.
- Involves comparison with an older active drug.

C. Phase III

- Done on large number of patients.
- Double-blind and cross-over techniques are frequently employed.

- After completion of Phase III, the drug company files a "new drug application" to the regulatory body.

D. Phase IV "Pharmacovigilance"

- Done to monitor the efficacy and safety of the new drug under actual conditions of use in large number of patients.
- It also involves "post-marketing surveillance" & post-licensing studies to determine additional efficacy & toxicity after general marketing.

Placebo

- The term "placebo" is Latin for "I shall please" referring to an inert substance given just to please the patient.

Placebo Effects

- The reactions unrelated to the pharmacologic effects of administered drug.

Placebo Responders

- People who respond excessively to placebo.

Uses of Placebo

1. **In therapeutics:** in psychotherapy, sometimes a placebo does as much good (and less harm) as a potent drug with serious toxic effects.
2. **In evaluation** of new drugs to avoid false conclusions:
    - To distinguish the pharmacodynamic effects of a drug from the psychological effects of the act of medication.
    - To distinguish drug effects from fluctuations in severity of disease.

Double-Blind Technique

- This technique was developed to prevent the effect of bias of both doctor and patient on results.
- The patient (the first "blind" man) does not know whether he is receiving the active drug or a placebo.
- The investigator (the second "blind" man) is ignorant of whether he is prescribing a placebo or an active drug.

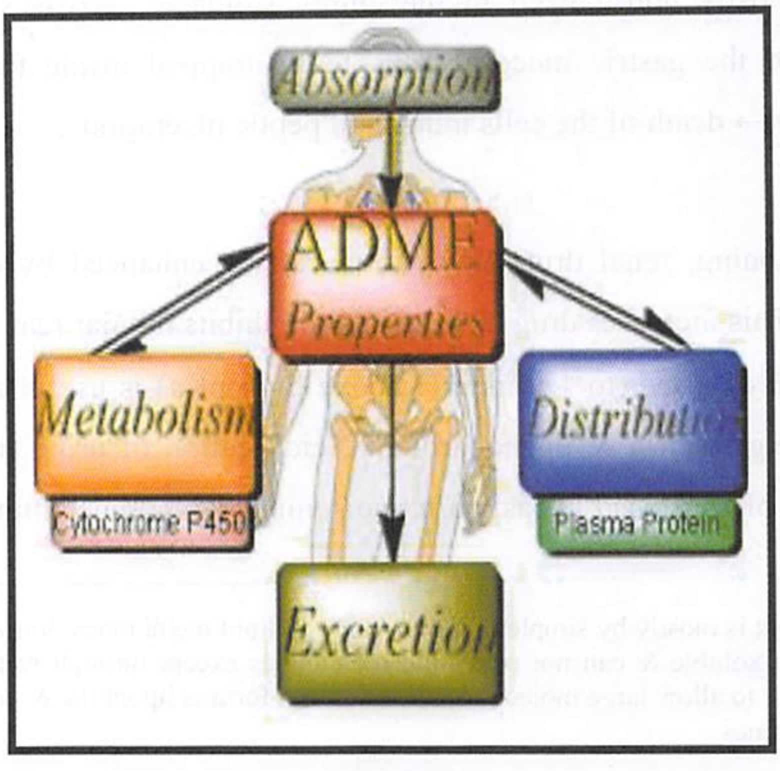
NB: In single-blind studies, only the patient is ignorant.

Cross-Over Trial

- It is conducted to protect against errors of interpretation caused by fluctuation in severity of disease.
- It consists of alternating periods of administration of test drug, placebo and standard drug control (to which the drug is compared).
- Each patient receives the three types of medications in a random sequence.

PHARMACOKINETICS

- The term pharmacokinetics denotes the quantitative studying of drug **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion **(ADME)** and their mathematical relationship.
- Studying the mathematical aspect of these items leads to calculation of pharmacokinetic parameters specific for each drug (e.g. bioavailability, volume of distribution, half life, clearance …etc.). These parameters can help the physician in adjusting dosage schedules of the drug for each individual patient based on its body characteristics.


Absorption
ADME
Properties
Metabolism
Cytochrome P450
Distribution
Plasma Protein
Excretion

ABSORPTION OF DRUGS

- Absorption is the passage of drug from the site of administration to the blood.

Lipid Diffusion[1]

- It is the most important means by which drugs enter the body and are distributed within it. It is dependent on the drug being lipid-soluble i.e. exists mainly in the non-ionized form.
- Ionization of the drug depends on the relation between its pKa and the pH of the surrounding medium:
  - When the pH of the medium = pKa of the drug; 50% of the drug molecules exist in the ionized form & 50% in the non ionized form.
  - Ionization of weak acids decreases at pH < pKa e.g. aspirin (pKa = 3.5) exists mainly in the non ionized (lipid soluble) form at gastric pH (1.5-2.5)
  - Ionization of weak bases decreases at pH > pKa e.g. theophylline (pKa = 8.8) is mostly non-ionized (lipid soluble) at alkaline pH of the intestine.

Clinical Significance of pK_a

1. GIT

Aspirin is mostly non-ionized in the empty stomach →crosses the cell membrane of the gastric mucosal cells to be trapped inside these cells (aspirin trap) → death of the cells inducing "peptic ulceration".

2. Kidney

In drug poisoning, renal drug elimination can be enhanced by changing urinary pH. This increases drug ionization and inhibits tubular reabsorption:

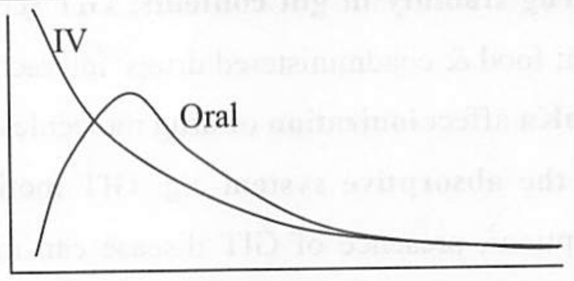
- Alkalization of urine (to ↑ urine pH above drug pKa) is useful in acidic drug poisoning e.g. aspirin & phenobarbital. Acidification of urine (to ↓ urine pH below drug pKa) is used in basic drug poisoning, e.g. amphetamine.

---

[1] Absorption of drugs is mostly by simple diffusion through lipid membranes. Ionized form of drug is water soluble & can not pass lipid membranes except through water filled pores (too narrow to allow large molecules). Non-ionized form is lipophilic & can easily cross lipid membranes.

Bioavailability (Biological Availability)

- It is the percentage of drug released from a formulation that reaches the systemic circulation and becomes available for biological effect.
- It is calculated by dividing the Area Under the blood concentration-time Curve (*AUC*) after any route of administration by that after IVI.



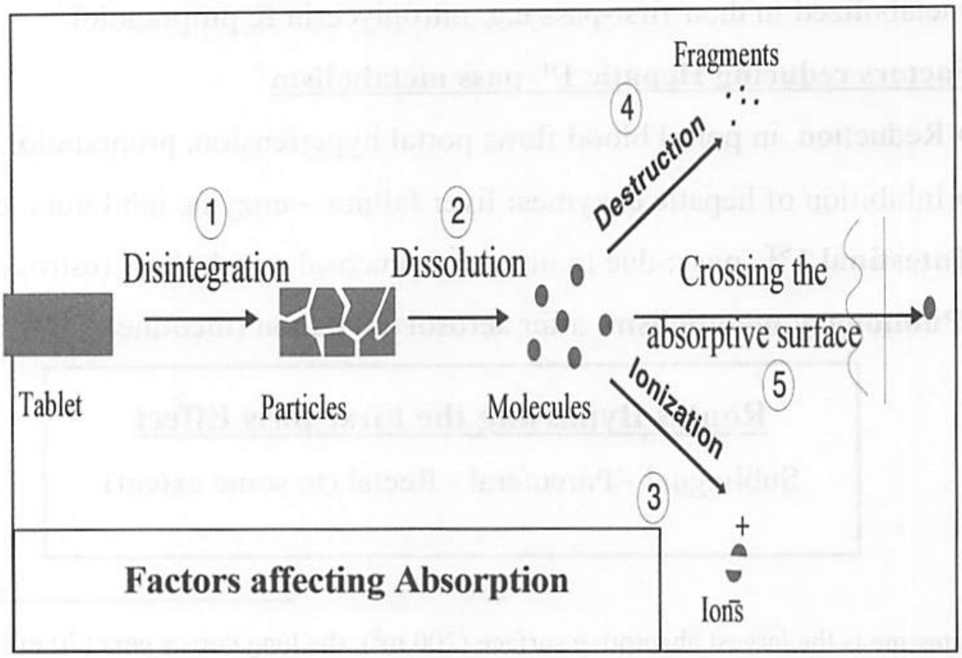
Concentration-Time curves after oral & IVI

Bioequivelance & Therapeutic equivalence:

- Two dosage forms are bio-equivalent if they have the same bioavailability & same time to achieve peak. They are therapeutically equivalent if they are bioequivalent & they have similar efficacy & toxicity profiles.

Factors Affecting Bioavailability:

- Factors affecting bioavailability include: **I.** Factors affecting drug absorption from GIT – **II.** First -Pass Effect


Fragments
④
Destruction
①
Disintegration
②
Dissolution
Crossing the
absorptive surface
Tablet
Particles
Molecules
⑤
Ionization
③
+
Ions
Factors affecting Absorption

I. Factors affecting drug absorption from GIT

1. **Factor related to dosage form** e.g. synthesis techniques & exipients added during preparation can affect disintegration of the dosage form into particles.
2. **Factor related to drug**: molecular weight, & solubility coefficient of the drug can affect the **dissolution** of the drug particles into molecules.
3. **Factor affecting drug stability in gut contents:** GIT secretions can result in drug destruction; food & coadministered drugs interact with drugs.
4. **Gut pH & drug's pKa** affect **ionization** of drug molecules into ions.
5. **Factor related to the absorptive system** e.g. GIT motility, surface area available for absorption[2], presence of GIT disease can modify the rate of crossing of the absorptive surface.

Drugs with variable bioavailability among different dosage forms

Digoxin - Phenytoin.

II. First-Pass Effect (First-Pass Metbolism; Presystemic Elimination)

- It is the metabolism of some drugs in a single passage through the liver, gut wall or the lungs before reaching the systemic circulation.

A. Hepatic first-pass effect: drugs absorbed from the GIT are carried first in the portal circulation to the liver. Some drugs are extensively metabolized in their first-pass e.g. nitroglycerin & propranolol.

Factors reducing Hepatic 1st pass metabolism

- Reduction in portal blood flow: portal hypertension, propranolol.
- Inhibition of hepatic enzymes: liver failure - enzyme inhibitors; erythromycin.

B. Intestinal 1ST -pass: due to intestinal mucosal metabolism (estrogen).

C. Pulmonary metabolism: after aerosol inhalation (nicotine).

Routes Bypassing the First-pass Effect

Sublingual - Parenteral - Rectal (to some extent)

---

[2] The intestine is the largest absorptive surface (200 m^2); the lung comes next (70 m^2).

DISTRIBUTION OF DRUGS

. After a drug is absorbed, it is distributed between blood and tissues. The drug passes through body compartments (plasma, interstitial, intracellular) which are separated by capillary walls and cell membranes.

Volume of Distribution (V_d)

- Drug distribution is interpreted mathematically as the apparent volume of distribution (V_d)[3].
- It is defined as the volume that would accommodate the entire amount of drug in body if its concentration throughout body was the same as that in plasma.

V_d = Amount of drug in the body/Plasma concentration

Factors affecting distribution of drugs:

- Drug distribution depends on: perfusion- diffusion- plasma protein binding-binding to tissue constituents- capillary permeability.

1. **Perfusion:** the amount of the drug which is delivered to a particular organ depends on the blood flow to that organ: ↑ blood flow → ↑ distribution.
2. **Diffusion:** the ability of the drug to diffuse across the cell membranes is governed by its liopphilicty: ↑ lipophilicity → ↑ distribution.

Significance of lipophilicity

- Lipophilicity facilitates drug absorption.
- Lipophilicity increases V_d, (lipophilic drugs can penetrate into most tissues e.g. CNS & placenta or enter the cells).
- Lipophilicity →↑ hepatic elimination (lipophilic drugs can enter hepatocytes).
- Lipophilicity →↓ renal excretion (due to ↑ tubular re-absorption).

---

[3] It is called apparent volume since it not a real volume

3. Binding to plasma proteins:

Drug in blood exists in 2 forms: **free form** & **plasma protein**[4] **bound form**:

- **Bound fraction** is inactive, nondiffusible, cannot be metabolized or excreted.
- **Free fraction** is active, diffusible and can be metabolized and excreted.
- The two forms exist in equilibrium; when the free form is metabolized and/or excreted, another part is released from plasma proteins.

Significance of Binding to Plasma Proteins

- Binding facilitates drug absorption by decreasing its free concentration in plasma.
- The binding of drug to plasma proteins limits its tissue penetration & decreases its V_d.
- The bound drug can not be eliminated and provides a reservoir which continuously releases the free part. This prolongs the $t_{½}$ of the drug.
- The concentration of the active or free part of highly protein-bound drugs may be too low to be effective against dangerous infections.
- Drugs which bind to the acidic binding site of albumin (low capacity binding site) can displace each other leading to clinically-significant drug interactions e.g. displacement of warfarin by aspirin →bleeding.

4. Binding to cell and tissue constituents:

It is due to an affinity to some cellular constituents. Examples:

- **Chloroquine** is concentrated in the liver.
- **Tetracyclines** deposit in bone and teeth as they chelate Ca^{2+}.
- **Iodides** are concentrated in thyroid and salivary glands.

---

[4] Plasma proteins responsible for drug binding: albumin (mainly) for acidic, neutral & basic drugs, globulins & α_1-acid glycoprotein (rarely) for basic drugs.

Importance of V_d

1. It is an estimate of the extent of tissue uptake of drugs:
    - Small V_d (e.g. frusemide) indicates that tissue uptake is limited.
    - Large V_d (e.g. digoxin) indicates extensive tissue distribution.
2. In cases of drug toxicity:
    - Dialysis is **not useful** for **high** V_d drugs (most of drug is in the tissues).
    - Dialysis is **useful** for **low** V_d drugs (most of drug is in blood and ECF).

- V_d can be used to calculate the loading dose (LD):

LD = V_d x Steady state plasma concentration (C_{ss})

Passage of Drugs to CNS

1. Lipid-soluble drugs pass freely through BBB, e.g. general anesthetics and other CNS depressants.
2. 2^{ry} & 3^{ry} amines can pass while 4^{ry} NH_4^+ compounds (ionized) cannot.
3. Dopamine cannot penetrate readily into CSF, so in parkinsonism we give levodopa, which can cross BBB and is decarboxylated to dopamine in brain.
4. Penicillins pass slightly through the normal barrier, but they penetrate readily in acute meningitis.
5. In tuberculous meningitis, INH, rifampin and pyrazinamide are effective as they can pass readily, but streptomycin cannot.

Passage of Drugs to the Fetus

- Many drugs cross placental barrier by simple diffusion (depending on their lipid solubility & their degree of ionization) and can harm the fetus:

1. Drugs given in 3rd to 10th week of pregnancy → teratogenicity
2. Morphine → respiratory depression (asphyxia neonatorum).
3. Oral anticoagulants → fatal hemorrhage in the newborn.
4. Oral hypoglycemics (sulfonylureas) → prolonged neonatal hypoglycemia.
5. Antithyroid drugs → neonatal goiter & hypothyroidism.
6. Aminoglycosides → 8th cranial nerve damage.

BIOTRANSFORMATION

(Metabolism)

- These are the changes that occur to drugs after absorption until excretion.
- Drug metabolism occurs mainly in the liver, though also in other organs, e.g. intestinal lumen or wall, lung, plasma, skin and kidney.

Consequences of Drug Metabolism

- The aim of drug metabolism is the conversion of the drug to a more polar (ionized) metabolite which is easily excreted. This may modify the activity of the drug in one of the following ways:
  - Abolishing the activity (occurs with most drugs).
  - Converting inactive prodrugs into active drugs, e.g. enalapril (to enalaprilat) & prednisone (to prednisolone).
  - Converting an active drug to another active one, e.g. codeine to morphine.
  - Converting drugs to a toxic metabolite e.g. paracetamol → toxic epoxide which is then conjugated with glutathione.

Types of Biotransformation Reactions

Phase I (Non-Synthetic)

- Phase I reactions include: oxidation - reduction - hydrolysis.
- The most important reaction is oxidation by cytochrome P450 enzyme system (mixed-function oxidases).
- Phase I reactions result in unmasking of a polar group (-OH, -SH, or -NH_2) → conversion of the drug to an ionized metabolite that can be easily excreted.

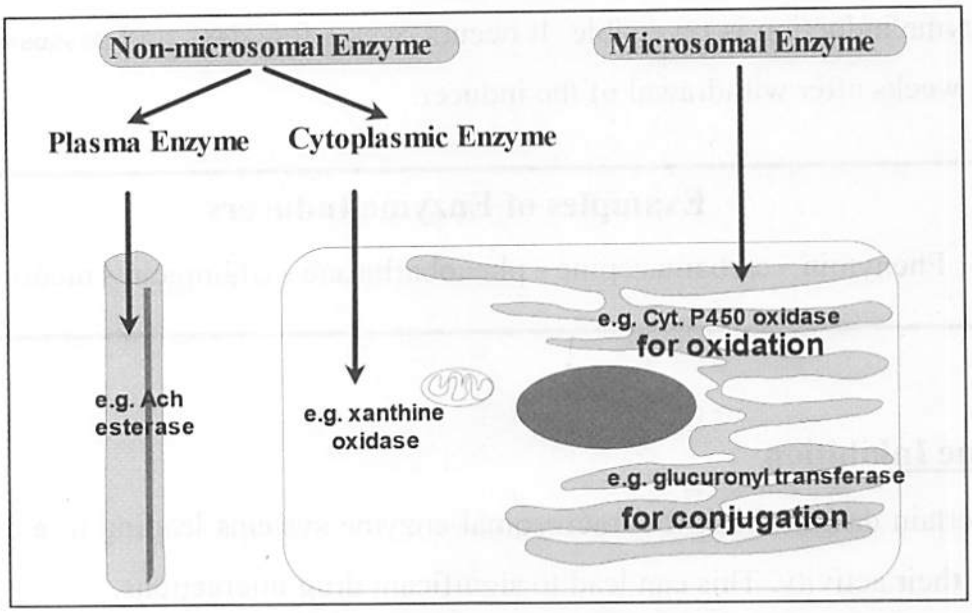
Phase II (Synthetic)

- An endogenous substrate, (e.g. glucuronic acid, glycine, glutathione, sulfate or acetic acid) is conjugated with the functional group of the drug or its metabolite (if the metabolite is still insufficiently polar). This results in the formation of non toxic highly polar, rapidly eliminated conjugates.

Types of Metabolizing Enzyme Systems

1. Microsomal enzymes e.g. cytochrome P450 oxidases for oxidation and glucuronyl transferase for conjugation

   Cytochrome P450 oxidases or simply "CYP". CYP is the most important metabolizing enzyme system. This enzyme system is further classified by family, subfamily & gene into many isozymes. The name of each one is designated by the term CYP followed by 3 characters e.g. CYP 3A4, which is responsible for metabolism of more than 35% of clinically important drugs[5].
2. Non-microsomal enzymes e.g. dehydrogenase & esterases.


Non-microsomal Enzyme
Microsomal Enzyme
Plasma Enzyme
Cytoplasmic Enzyme
e.g. Ach esterase
e.g. xanthine oxidase
e.g. Cyt. P450 oxidase
for oxidation
e.g. glucuronyl transferase
for conjugation

Factors Affecting Biotransformation

1. Physiological changes in metabolizing activity due to age & sex.
2. Pathological factors which affect hepatic activity e.g. liver cell failure.
3. Pharmacogenetic variations in metabolizing enzymes e.g. slow & fast acetylators (see pharmacogenetics).
4. Enzyme induction[6] & enzyme inhibition.

---

[5] The first Arabic numeral represents the family, the alphabetic letter represents the subfamily, the second Arabic numeral represents the individual gene within the subfamily.

[6] Enzyme induction is not a phenomenon related to drugs only but can also occur with many chemical substrates and a useful mechanism for adaptation to environmental pollution .

Enzyme Induction:

- Certain drugs stimulate the microsomal enzyme systems leading to an increase in their activity →
  - Increase metabolism of the inducing drugs (this leads to tolerance e.g. phenobarbitone).
  - Increase the metabolism of other drugs metabolized by these enzymes (this leads to drug interactions e.g. rifampicin →↑ warfarin metabolism).
  - Increase the metabolism of endogenous substrates (e.g. phenobarbitone may be used to enhance the elimination of bilirubin in case of neonatal jaundice)
- Enzyme induction is reversible. It occurs over a few days and passes off over 2-3 weeks after withdrawal of the inducer.

Examples of Enzyme Inducers

Phenytoin - carbamazepine - phenobarbitone - rifampicin - nicotine.

Enzyme Inhibition:

- Certain drugs inhibit the microsomal enzyme systems leading to a decrease in their activity. This can lead to significant drug interactions.
- It occurs faster than enzyme induction.

Examples of Enzyme Inhibitors

Chloramphenicol - erythromycin - ciprofloxacin - ketoconazole.

EXCRETION OF DRUGS

- The **kidney** is the most important route of excretion. Excretion occurs through:

1. **Glomerular filtration:** molecules whose size are < the glometular pores.

Factors affecting glomerular filtration

- Glomerular filtration rate (GFR)
- Plasma protein binding (PPB) → prevents filtration
- Drug Lipophilicity (affected by pH of urine & pKa of the drug) → enhances reabsorption of the drug after being filterated.

2. **Active tubular secretion**: either through acid carrier e.g. for penicillins, probenecid, salicylic acid, or basic carrier e.g. for amphetamine, quinine.

- **Other sites for excretion**
  - **Lungs** e.g. volatile anesthetics
  - **Saliva**: e.g. iodides
  - **Bile**: e.g. rifampicin
  - **Milk**: this is important for lactating mothers [7]

Drugs Contraindicated During Breast Feeding

1. Antibiotics: chloramphenicol, tetracyclines, sulfonamides.
2. CNS drugs: narcotics, benzodiazepines, alcohol, nicotine.
3. Laxatives as cascara and senna.
4. Corticosteroids (suppress fetal growth).
5. Bromocriptine & sex hormones (suppress lactation).

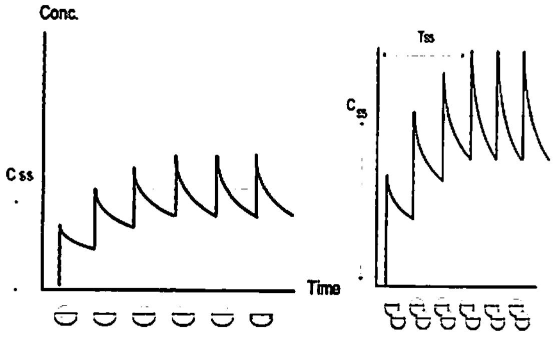
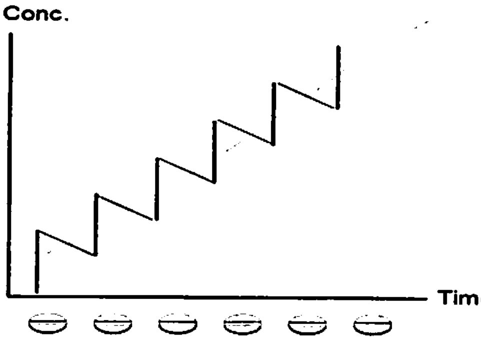
N.B.: To ↓risk to infants, lactating mothers should take drugs immediately after nursing and/or 3-4 hrs before the next feeding.

---

[7] pH of milk is more acidic than that of plasma → basic drugs accumulate in milk. Milk contains more fat → retention of lipid soluble drugs e.g. cytotoxics, metronidazole, morphine, laxatives.

PARAMETERS OF ELIMINATION

1. Kinetic orders

A. First order kinetics	B. Zero order Kinetics
• A constant **fraction** of drug is eliminated per unit time, e.g. 50%/ h. • Rate of elimination varies & is proportional to drug concentration as metabolizing enzymes have high capacity.	• A constant **amount** of drug is eliminated per unit time, e.g. 50 mg/h. • Rate of elimination is constant, even if drug concentration changes, since metabolizing enzymes have limited capacity.
• Constant t½.	• t½ is not constant
• On repeated dosing; a steady state concentration[8] (C_{ss}) is reached. • $C_{ss} \propto$ dose. • T_{ss} (time to reach C_{ss}) ≈ 4-5 $t_{1/2}$[9]  ↑ dose → ↑ Css	• No C_{ss} is reached; repeated dosing result in overshooting of drug concentration. 
• Modest changes in dose or bioavailability →are usually tolerated.	• Modest changes in dose or bioavailability → toxicity.
• Drug metabolites do not vary with dose.	• Drug metabolites may vary with dose[10]
• Examples: Most drugs.	• Famous example: ethanol[11].

---

[8] Repeated dosing →↑ drug concentration & accordingly the rate of elimination increases till the rate of administration becomes equal to the rate of elimination. At this point the Css is reached

[9] After 4 t½ ; > 95% of the Css is attained

[10] Increasing dose of drug → depletion of metabolizing enzymes with diversion of drug to other metabolic routes giving different metabolites

[11] Most zero order kinetic drugs are excluded from the market for safety concerns.

C. Saturation kinetics

- The drug follows first order kinetics if it is eliminated by very active or non restricted mechanism e.g. glomerular filtration or metabolism with very active enzyme. If the elimination mechanism has very limited activity; the drug follows zero order kinetics.
- Sometimes the elimination mechanism is in between; in such case the drug follows first order kinetics at small dose & zero order kinetics at large doses.The elimination mechanism is said to be saturated and this type of kinetics is termed saturation kinetics.

Significance of saturation kinetics:

- Modest changes in dose or bioavailability of drugs → unexpected toxicity.
- Drug interactions are more common.

Drugs with Saturation kinetics

Phenytoin.

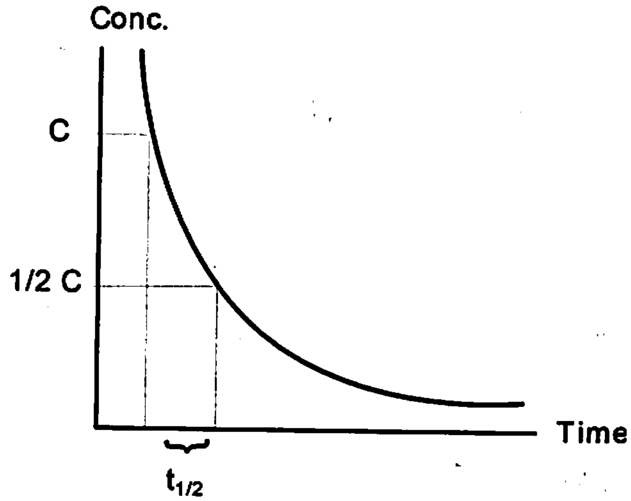
Theophylline

2. Elimination half life ($t_{1/2}$)

Definition

- It is the time required to reduce the plasma concentration of drug to half the initial concentration:

$$t_{1/2} = 0.693\ V_d\ /\ CLs$$ [12]



Value of elimination t½

1. It determines the dosage interval (τ).
   - If $\tau = t_{½}$ → body stores twice the dose (for most drugs, this is an accepted choice [13]).
   - If $\tau < t_{½}$ → more drug accumulation occurs.
   - If $\tau > t_{½}$ → decrease in drug concentration occurs between doses.
2. It indicates T_{ss} (time required to attain Css): about 4- 5 t½.

Factors affecting elimination t½

1. The state of the eliminating organs i.e. liver & kidney functions
2. The delivery of the drug to the eliminating organs e.g.:
   a. Plasma protein binding limits renal filtration.
   b. Drugs with very high V_d may escape from elimination in the tissues.

---

[12] Elimination half-life = ln ½ /Ke; ln½ =0.693 & Ke is the elimination rate constant = Cls/Vd where Cls is the systemic clearance.

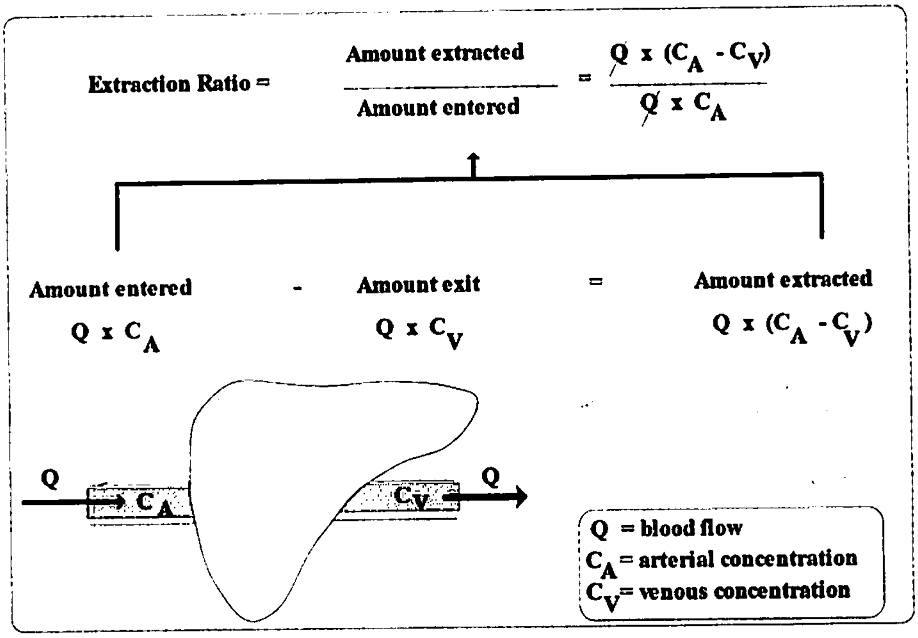
[13] For drugs with too short $t_{1/2}$; we may resort to IV infusion or slow release (SR) oral preparations.

3. Extraction ratio (E) & Hepatic clearance (Cl_{liver})

Extraction ratio (E)

- It is the fraction of the drug eliminated by the liver.

E = (Arterial drug conc.) - (Venous drug conc.) / (Arterial drug conc.)



Extraction Ratio = Amount extracted / Amount entered = $\frac{Q \times (C_A - C_V)}{Q \times C_A}$
Amount entered
$Q \times C_A$
-
Amount exit
$Q \times C_V$
=
Amount extracted
$Q \times (C_A - C_V)$
Q
C_A
C_V
Q
Q = blood flow
C_A = arterial concentration
C_V = venous concentration

- When E is > 0.7 → clearance is nearly *flow-dependent*, e.g. propranolol.
- When E is < 0.2 → clearance is nearly *enzyme-dependent*, e.g. warfarin
- When E is 0.2-0.7 → clearance is both flow and enzyme dependent, e.g. acetaminophen, chloramphenicol

Hepatic clearance (Cl_{liver})

- It is the volume of blood cleared by the liver per unit time:

Cl_{liver} = Extraction ratio (E) x Hepatic blood flow (Q)

4. Systemic clearance (CLs)

Definition

- It the volume of a fluid cleared from the drug per unit time.

CLs = Rate of elimination/Drug concentration

- The systemic clearance is equal to the sum of individual organs clearances i.e. the clearnce by the liver, kidney, lung, ….etc.

Cls = renal clearance (*Clr*) + non-renal clearance (*Clnr*)

Factors affecting drug clearance

1. Blood flow to the clearing organ (directly proportional).
2. Binding of the drug to plasma proteins (inversely proportional).
3. Activity of processes responsible for drug removal as hepatic enzymes, glomerular filtration rate and secretory processes (directly proportional).

Significance of clearance

1. Calculation of the maintenance dose (MD):

   MD = CLs x Steady state plasma concentration (C_{ss})

2. The dosing regimen of drugs eliminated by glomerular filtration can be guided by creatinine clearance e.g. dosing of gentamicin
   - If Kidney function is normal (Cr Cl=120 ml/min): 80 mg 3 times /day
   - If the kidney function is impaired you can reduce the dose or increase the dose interval according to the level of Cr Cl:
     - If CrCl = 60 ml/min: give half the usual dose (i.e. 40 mg three times/day) or give the usual 80 mg dose every 16 hours
     - If CrCl = 30 ml/min: give one quarter the usual dose (i.e. 20 mg three times/day) or give the usual 80 mg dose every 32 hours

PHARMACODYNAMICS

Mechanism (Mode) of Action of Drugs

- Drugs can induce a tissue response, initially through:
  - I. Receptor-mediated mechanisms involving interactions with particular receptors at specialized sites within the body.
  - II. Non-receptor-mediated mechanisms.

1. Receptor-Mediated Mechanisms

- **Receptors**[14] are specific cellular macromolecules (usually proteins) that interact with a ligand (**binding**) to produce a response.

Ligands binding

Types of ligands

1. Full Agonist

Interacts with the receptor (affinity) activating it (efficacy) → pharmacologic effect, i.e. it has **affinity and efficacy**, e.g. acetylcholine (Ach) activates nicotinic receptors → depolarization → skeletal muscle contraction.

2. Partial Agonist (Agonist-Antagonist)

- In absence of the agonist, it activates the empty receptor, but with lower efficacy than that of a full agonist.
- In the presence of the agonist, it acts as an antagonist.

Example: Buprenorphine is a partial agonist for opioid receptors. In the absence of a pure agonist e.g. morphine, it exhibits analgesic effects. In the presence of morphine it acts as an antagonist reducing its analgesic effect.

---

[14] The pharmacological actions mediated by the receptors are characterized by **sensitivity** (i.e. very small conc. of ligand is enough to elicit the action), **selectivity** (i.e. each receptor has the type of ligand that can interact with it) & **specificity** (i.e. they elicit the same response each time they interact with ligand).

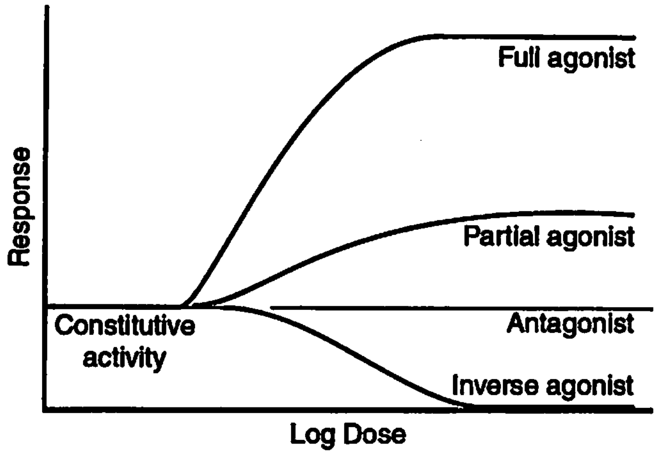
3. Inverse agonist

- Stabilizes receptor away from the constitutional conformation[15].
- Produces a response opposite to the pharmacological effect of the agonist.

Example: some anti-histamines[16]

4. Antagonist

- Interacts with the receptor without activation (**affinity without efficacy**), e.g. curare blocks nicotinic receptors → prevents depolarization by Ach → relaxation. There are 2 types of receptor antagonists:
- **Competitive antagonists**: **compete** with agonists for the same recognition site of the receptors → the agonist behaves as if it were less potent.
- **Noncompetitive antagonists**: **prevent binding** of the agonist or **prevent activation** of the receptor by the agonist.

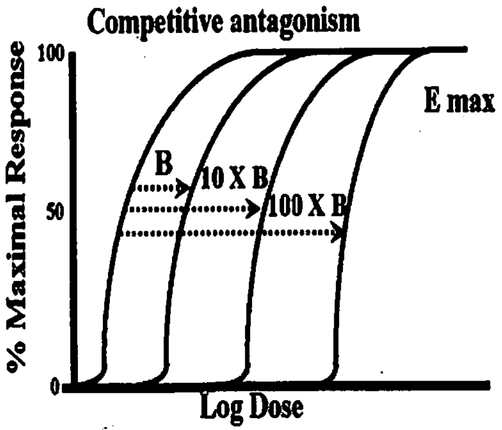
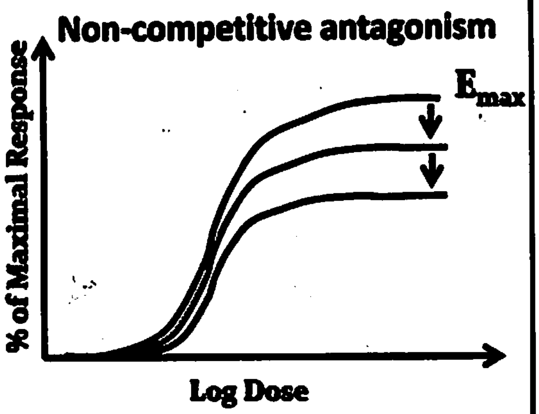


---

[15] The three-state model of receptor activation suggests that receptors exist in 3 conformational states, inactive, active & constitutional states that are in a reversible equilibrium. The constitutional state has some activity even in absence of ligand binding. In the presence of an agonist, the receptors are in the active state, and in presence of the antagonists, they become in the inactive conformational state. The inverse agonist shifts equilibrium away from the constitutional state.

[16] Other inverse agonists include beta carboline

Comparison between Competitive & Noncompetitive Antagonists

Competitive Antagonist	Noncompetitive Antagonist
• Antagonist competes with the agonist for the same recognition site of the receptor.	• Antagonist binds irreversibly to the recognition site of the receptor or bind to an allosteric site.
• Duration of antagonism depends on the relative plasma concentrations of agonist and antagonist.	• Duration of antagonism depends on the rate of turnover of the receptor molecules.
• Causes parallel shift to the right in the log dose-response curve with increase in the EC_{50} but no change in E_{max} (maximum response).	• Causes downward shift in log dose-response curve with decrease in E_{max} (maximum response) but no change in EC_{50}.
 Competitive antagonism 	 Non-competitive antagonism
• Examples: Curare (Nm blocker).	• Example: Phenoxybenzamine (α blocker).

N.B. :

The action of a ligand can also be reversed by non-receptor antagonists e.g.:

- **Chemical antagonists**: interact chemically with the agonist away from receptor, e.g. negative charges on heparin are neutralized by positive charges on protamine sulfate (heparin antidote).

- **Physiological antagonists**: one drug antagonizes the effect of another by acting on a different receptor to induce the opposite action e.g. β_2-bronchodilator and alpha vasoconstrictor effects of epinephrine antagonize H_1-bronchconstrictor and vasodilator effects of histamine.

Receptor Cycling or Turnover

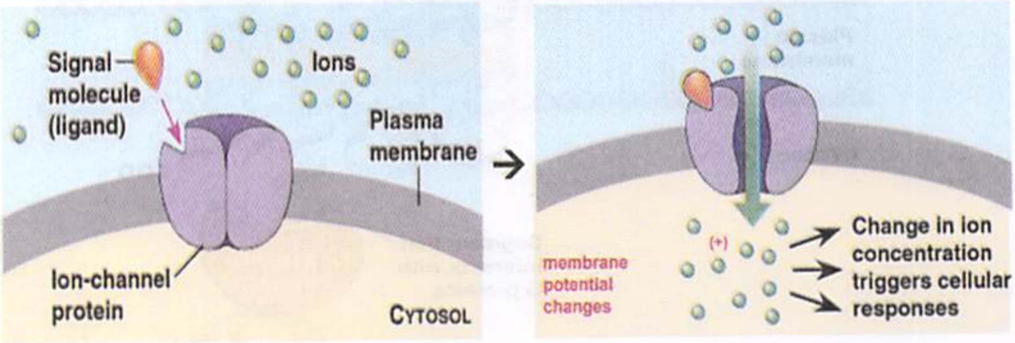
- The number of receptors is not constant but the receptors are cycling (old receptors are internalized inside the cell and the new ones are externalized to the outside) and their number is continuously changing depending on the rate of recycling.
- Binding of the agonist → increases receptor internalization → ↓ number of recruited receptors [**down regulation**] while binding of the antagonist → ↑ the number of recruited receptors [**up regulation**].

SIGNALING MECHANISMS

- The most important signal transduction systems are:

1. **Ion Channels** (for fast neurotransmitters)
   - Receptors are ion-selective channels in the plasma membrane.

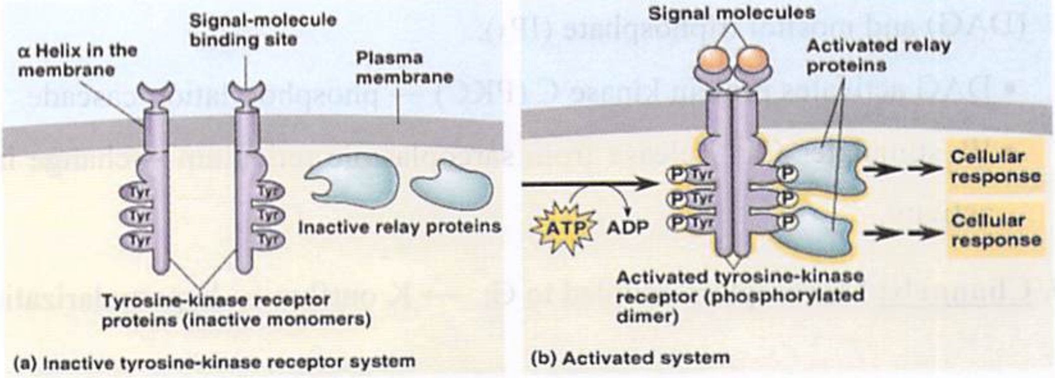
     Binding of agonist to the receptor →opening of the channel → alteration in membrane potential or change in intracellular ion concentration, both resulting in change in cell activity, e.g. nicotinic Ach receptors (combined Na^+/K^+ channels) – $GABA_A$ receptors (Cl^- channels).


Signal molecule (ligand)
Ions
Plasma membrane
Ion-channel protein
CYTOSOL
(+)
membrane potential changes
Change in ion concentration triggers cellular responses

2. **Receptors *linked to* Tyrosine Kinase (RTKs)**
   - The receptor is formed of two domains:

     a. An extracellular domain, to which the agonist (e.g. insulin) binds.

     b. An intracellular domain, which is a tyrosine kinase enzyme (effector).
   - Binding of insulin causes 2 single tyrosine-kinases receptors to aggregate into a dimmer with subsequent autophosphorylation. Then, the activated-phosphorylated dimmer binds to relay proteins, activating them. These relay proteins trigger the cellular response through either production of a second messenger or turning on gene expression.

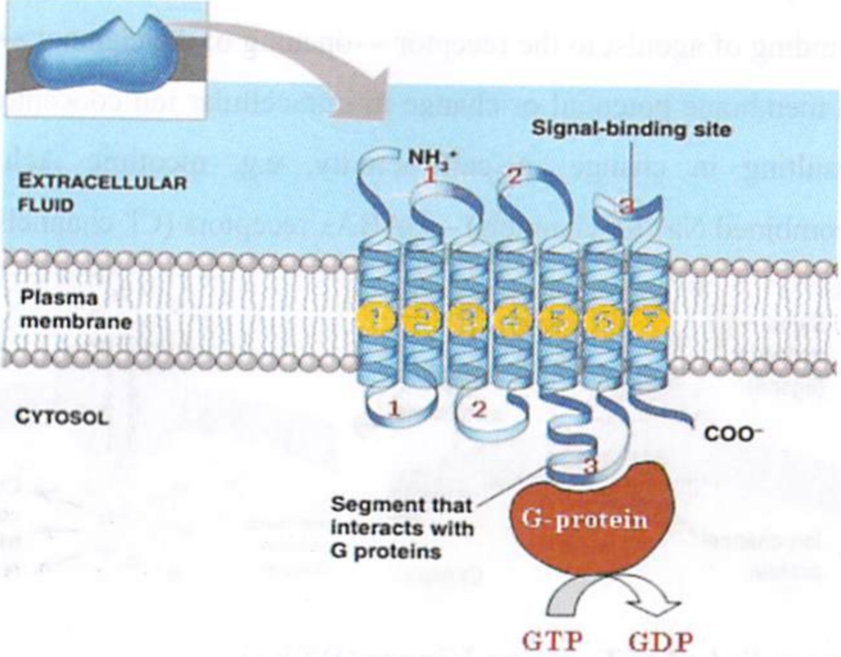

α Helix in the membrane
Signal-molecule binding site
Plasma membrane
Tyr
Tyr
Tyr
Tyr
Tyr
Tyr
Inactive relay proteins
Tyrosine-kinase receptor proteins (inactive monomers)
Signal molecules
Activated relay proteins
ATP
ADP
P Tyr
P Tyr
P Tyr
P
P
P
Cellular response
Cellular response
Activated tyrosine-kinase receptor (phosphorylated dimer)

(a) Inactive tyrosine-kinase receptor system

(b) Activated system

3. G protein-Coupled Receptors (for slow neurotransmitters)

- Receptors are linked to G proteins. The G protein is a trimer (α, β and γ).
- Agonist binding → dissociation of α subunit which **regulates** activity of several effectors.


Signal-binding site
NH$_3^+$
1
2
3
EXTRACELLULAR FLUID
Plasma membrane
1
2
3
4
5
6
7
CYTOSOL
1
2
3
COO⁻
Segment that interacts with G proteins
G-protein
GTP
GDP

Examples of G Proteins

a. **G_s** (stimulatory) linked to β-receptors resulting in increased cAMP.

b. **G_i** (inhibitory) linked to α_2 and M_2 receptors resulting in decreased cAMP.

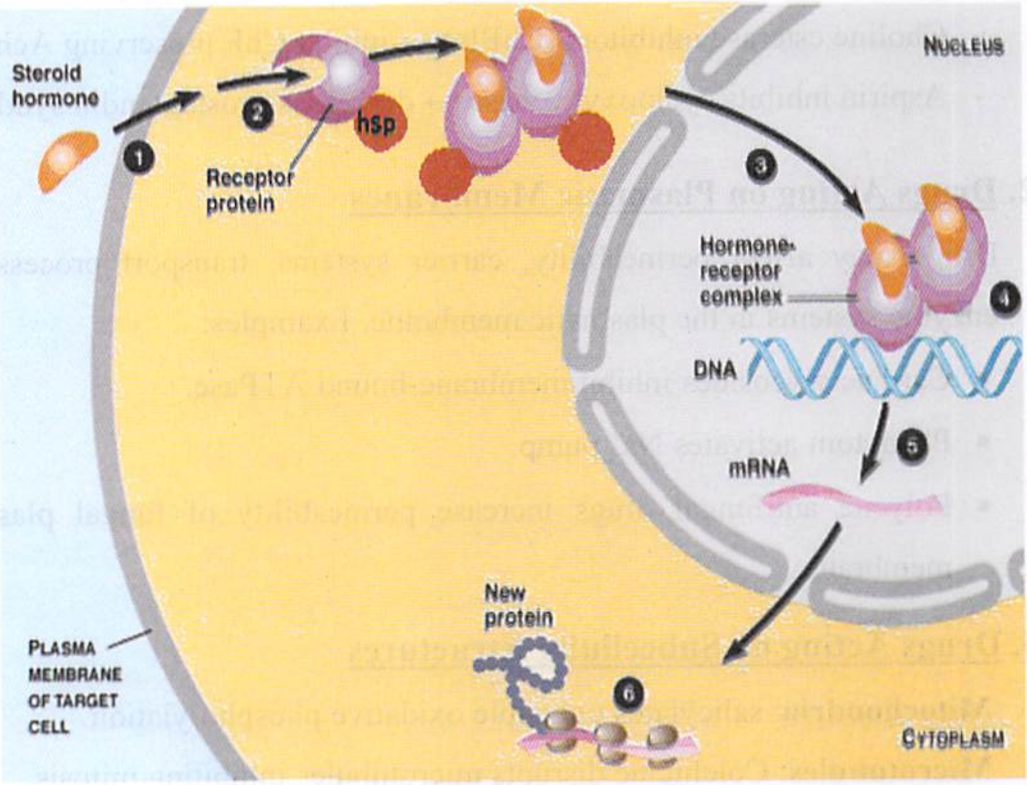
c. **G_q** linked to α_1 and M_1 & M_3 receptors liberating DAG and IP_3.

Effectors Regulated by G proteins

1. **Adenylyl cyclase**, which forms the second messenger cAMP which activates protein kinase A (PKA) with subsequent phosphorylation cascade.
2. **Phospholipase C**, which liberates the second messengers: diacyl-.glycerol (DAG) and inositol triphosphate (IP_3):
   - DAG activates protein kinase C (PKC) → phosphorylation cascade.
   - IP_3 stimulates Ca^{2+} release from sarcoplasmic reticulum →change in cell activity.
3. **Channels:** M_2 receptors coupled to G_i → K outflux → hyperpolarization

4. Receptors Regulating Transcription (very slow)

- Steroid hormones, estrogen, progesterone, thyroid hormones and vitamin D enter the target cell and combine with intracellular receptor proteins associated with nuclear chromatin (DNA) to activate or inhibit transcription of the nearby gene. This will modify protein production and cause changes in the structure or function of the target tissue.


Steroid hormone
1
2
Receptor protein
hsp
NUCLEUS
3
Hormone-receptor complex
4
DNA
5
mRNA
New protein
6
PLASMA MEMBRANE OF TARGET CELL
CYTOPLASM

5. Nitric Oxide (NO) Receptors:

- NO receptors are protein receptors inside the cell. Binding of NO triggers an allosteric change in the protein, which in turn, triggers the formation of a "second messenger" within the cell. The most common protein receptor for NO seems to be soluble guanylyl cyclase enzyme that generates the second messenger cyclic GMP (cGMP).
- NO receptors are activated by many drugs that increase NO level e.g. nitrovasodilators (nitrites, nitrates as nitroglycerine & sodium nitroprusside) & muscarinic M_3-agonists (release endothelial NO). The action can also be mimicked by the phosphodiesterase inhibitors (e.g. sildenafil), which increase the level of the second messenger c-GMP.

II. Nonreceptor-Mediated Mechanisms

1. Drugs Acting on Enzymes

- Drugs may inhibit or activate enzyme systems.
- Examples of drugs acting via enzyme inhibition:
  - Monoamine oxidase inhibitors (MAOIs) → inhibit MAO enzyme preventing destruction of biogenic amines (e.g. norepinephrine).
  - Choline esterase inhibitors (ChEIs) → inhibit ChE preserving Ach.
  - Aspirin inhibits cyclooxygyenase → decreases prostaglandin synthesis.

2. Drugs Acting on Plasmatic Membranes

Drugs may affect permeability, carrier systems, transport processes or enzyme systems in the plasmatic membrane. Examples:

- Cardiac glycosides inhibit membrane-bound ATPase.
- Phenytoin activates Na^+ pump.
- Polyene antifungal drugs increase permeability of fungal plasmatic membrane.

3. Drugs Acting on Subcellular Structures

Mitochondria: salicylates uncouple oxidative phosphorylation.

Microtubules: Colchicine disrupts microtubules inhibiting mitosis.

4. Drugs Acting on the Genetic Apparatus

- Antibiotics (e.g. aminoglycosides, chloramphenicol & tetracyclines) inhibit bacterial protein synthesis.
- Anticancer drugs affect DNA synthesis or function, e.g. antimetabolites and alkylating agents.

5. Drugs Acting by Physical Means

- **Demulcents** (soothing): bismuth salts coat intestinal mucosa.
- **Adsorbents**: charcoal adsorbs gases and toxins in intestine.
- **Lubricants**: liquid paraffin is used in constipation.
- **Osmosis**: osmotic diuretics.

6. Drugs Acting by Chemical Action

a. Antacids neutralize HCL in peptic ulcer.

b. Citrates interact with calcium to inhibit blood coagulation.

c. Protamine neutralizes heparin by its positive charge in treatment of heparin overdose.

d. Chelation; is the capacity of organic compounds to form complexes with metals (chelates). The chelate may become more water-soluble and easily excreted. It is useful in treatment of heavy metal poisoning:

Examples of Chelators

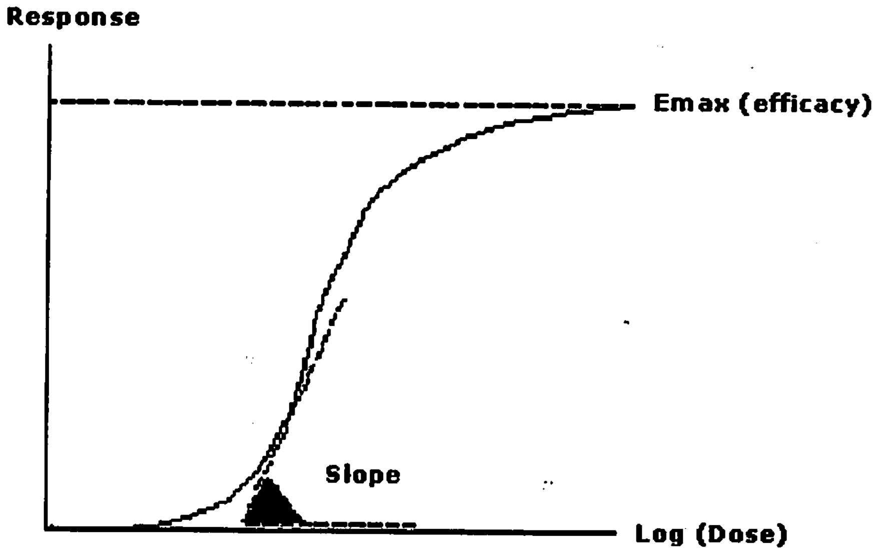
1. **Ethylene diamine tetra acetic acid (EDTA)** chelates lead & calcium.
2. **Dimercaprol (BAL)** chelates arsenic, gold & copper.
3. **Penicillamine** chelates copper in Wilson's disease.
4. **Desferrioxamine** chelates iron and is used in iron toxicity.

Dose-response Relationship

Dose-response curves

- The dose-response relationship can be represented graphically by 2 types of curves: the quantitative (graded) dose-response curve and the qualitative (All/None) dose-response curve:

I. Graded dose-response curve is obtained if the degree of response is depicted against log the dose e.g. decreases of blood glucose against the dose.



Parameters that can be obtained from the graded dose-response curve:

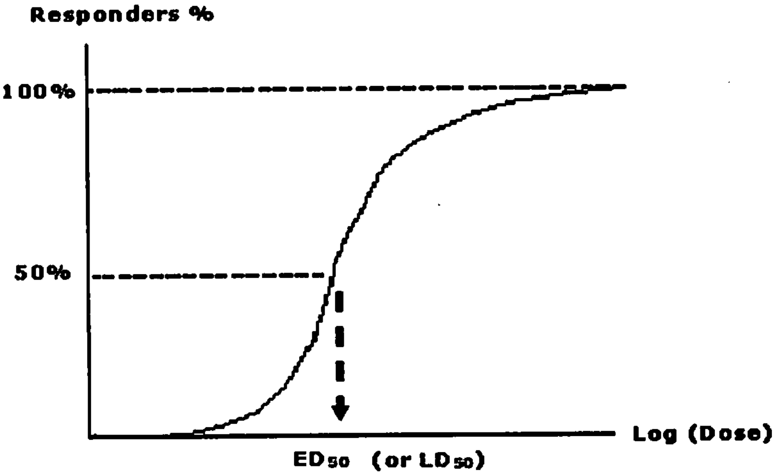
1. **Efficacy (Emax)**: is the maximal effect produced by the drug *(= the maximum value of the dose-response curve)*

2. **Potency** of the drug is assessed from 2 parameters:
   a. **ED_{50}:** it is dose that produces 50% of the maximal response and is estimated similar to the "All or none curve". The lower the ED_{50} the more potent the drug is. [17]
   b. **Slope** of the middle portion of the curve (it reflects the effect of the drug produced by one unit of the dose. The steeper the curve (i.e. the higher the slope) the more potent the drug is.

---

[17] It should be noted that low ED_{50} means a more potent drug but it does not essentially mean a more effective drug; efficacy of the drug is assessed by the Emax and not the ED_{50}.

II. **All/None dose-response** curve is obtained if the percentage of patients who respond to the drug is depicted against log the dose e.g. the % of patients in whom the arrhythmia is terminated by different doses of an antiarrhythmic drug



Parameters that can be obtained from the All/None curve:

1. **ED_{50}:** It is the dose that cures 50% of cases. It is used for comparison between drugs e.g. drug with a lower ED_{50} is > potent than that with a higher ED_{50}.
2. **LD_{50}:** If we draw the relation between the % **mortality** in animals treated by the drug (rather than the % responders) and the log of the dose, we will obtain the LD_{50} (the dose that kills 50% of animals) instead of ED_{50}. LD_{50} gives an idea about the absolute toxicity of the drug i.e. the drug with lower LD_{50} is considered more toxic than the drug with higher LD_{50}. The dose used should not exceed 10% of the estimated LD_{50}.
3. **Therapeutic index (TI):**
    - It is the ratio between ED_{50} & LD_{50} → $TI = LD_{50}/ED_{50}$.
    - It gives an idea about the safety of the drug: if the TI is large, i.e. the LD_{50} is much higher than the ED_{50} → the drug is safer.

Drugs with narrow therapeutic index:

- Aminoglycosides, anticoagulants, antiepileptics, hypoglycemic agents, lithium, quinidine, theophylline and tricyclic antidepressants.

Factors Modifying Dose-Response Relationship

- The dose is the main factor modifying drug action. Other factors include:

[1] Age:

- Younger patients can not tolerate the adult dose; accordingly the dose of the drug for the children should be reduced.
- Various methods & formulas are used for calculating the child dose:
  - a. **Surface area method:**
    The child dose = Adult dose X Surface area (m^2)/ 1.73
  - b. **Age method:**
    The child dose =-Adult dose X Age (years) / age + 12
  - c. **Weight method:**
    The child dose = Adult dose X Weight (Kgs) / 70
  - d. **Percentage method:**
    The dose is calculated as a percent of adult dose:

1 month (12.5%)	2 month (15%)	1 year (25%)
2 years (33%)	7 years (50%)	12 years (75%)

[2] Sex:

- Certain drugs act specifically in the female organs e.g. sex hormone (estrogen & progesterone), ergot alkaloids & oxytocin
- In pregnant female: → some drugs can cause teratogenicity e.g. thalidomide & antithyroid drugs.
- In lactating female: some drugs can pass to the fetus in milk e.g. ephedrine & phenobarbitone.

[3] Pathological States:

- The presence of certain disease may make the patient more sensitive to certain drugs e.g.
  - In bronchial asthma: ß-blockers → asthmatic attack.
  - In myasthenia gravis: competitive skeletal muscle relaxants and quinine → myasthenic attack

[4] Tolerance:

- It is reduced responsiveness to the drug on repeated administration so that higher doses are needed to produce the same effect.

Pharmacokinetic tolerance: is tolerance due to decreased drug level at the site of action. For example: enzyme induction increases the liver capacity to metabolise the drug (e.g. with the anti-epileptic drugs phenytoin and phenobarbitone) which may lead to decrease in their effects.

Pharmacodynamic tolerance: *is tolerance without decreased drug level e.g.*

- Decreased sensitivity of the receptors e.g. opiates
- Decreased number of receptors [down regulation] e.g. β_2-agonists
- Increased number of receptors [up regulation] e.g. H_2-receptor antagonists.
- Depletion of neurotransmitters e.g. dopamine with amantadine
- ↑ release of the neurotransmitter e.g. ↑ Ach release with ipratropium
- Counter regulatory mechanism e.g. salt &water retention with vasodilators.

Special types of tolerance:

a. **Tachyphylaxis:** acute tolerance but the same effect can not be obtained by ↑dose e.g. tolerance due to depletion of NE from few doses of ephedrine.

b. **Cross tolerance**: tolerance to related drugs e.g. cross tolerance between different members of opioids.

[5] Psychological factors:

- Some patients may respond to a **placebo** the same way they respond to the active drug. The placebo may be used for psychological therapy & in control studies to differentiate true drug effect from that 2^{ry} to psychological factors

[6] Drug interactions:

- The response to the drug may be affected by administration of another drug:

  Antagonism: decreased response by a second drug.

  Enhancement: summation, synergism and potentiation: increased response in the presence of a second drug (see drug interactions).

ADVERSE DRUG REACTIONS

- The term "adverse reactions" is used for harmful effects of a drug, which require reduction of dose, drug withdrawal or immediate treatment.

Types of Adverse Reactions

Type A: Augmented (side effects and overdose toxicity).

Type B: Bizarre (hypersensitivity, idiosyncrasy).

Type C: Continuous (reactions due to long-term use).

Type D: Delayed (teratogenesis and carcinogenesis).

Type E: Ending of use (adverse effects following drug withdrawal).

Type A (Augmented)

a. **Intolerance** (at doses < therapeutic): tinnitus after a single, small aspirin dose due to lower threshold to a normal pharmacologic action of drug.

b. **Side effect (occurs at therapeutic dose) e.g.**

   i. **1^{ry} pharmacological action e.g.** dry mouth from antihistamines.

   ii. **2^{ry} pharmacological action e.g.** thrush[18] while taking antibiotics.

c. **Overdose** (at doses slightly > therapeutic): seizure with lidocaine.

d. **Toxic effect (at very high doses) e.g.** hepatotoxicity with acetaminophen.

Type B (Bizarre)

1. **Hypersensitivity (Allergic reactions)**

   - Immune-based adverse reactions. They are not dose-related but are induced by prior contact with drugs that act as antigens.

2. **Idiosyncrasy**

   - Genetically-mediated adverse effects e.g. porphyria, favism (see pharmacogenetics).

Type C (Continuous)

- Adverse effects occurring on chronic use of drugs e.g. analgesic nephropathy or corticosteroids-induced osteoporosis, diabetes and hypertension.

---

[18] Due to overgrowth of candidal infection.

Type D (Delayed):

- This adverse effect may occur even after stopping drug. There are 3 types
  a. **Mutagenicity:** drug-induced gene abnormalities; with metronidazole.
  b. **Carcinogenicity:** drug-induced neoplasm; with alkylating agents - radioactive drugs.
  c. **Teratogenesis** (teratos = monster; genesis = production): induction of fetal abnormalities. It can be caused by some drugs when given early in pregnancy. The most vulnerable period is weeks 3-10 of intrauterine life.

Teratogenic drugs	
• Thalidomide: phocomelia.	• Cytotoxic drugs: fetal anomalies
• Tetracyclines: dental hypoplasia.	• I131: fetal goiter
• Sex hormones (oral contraceptives).	• Antiepileptics: cleft palate
• Adrenal steroids	• Alcohol - smoking

Type E (adverse effects following withdrawal of some drugs)

1. **Abstinence (withdrawal syndrome)** in drug-dependent persons (addicts) following withdrawal of narcotics, alcohol, hypnotics...
2. **Addisonian crisis** on sudden withdrawal of chronic corticosteroid therapy.
3. **Angina or infarction** may follow sudden withdrawal of β-adrenoceptor blockers (due to upregulation of β-adrenoceptors → ↑ heart activity).
4. **Hypertension** and sympathetic over-activity on clonidine withdrawal.
5. **Thromboembolism** following withdrawal of oral anticoagulants.

Other Adverse Effects

1. **Drug Abuse:** the use of a drug for non-therapeutic purpose. It is more common with drugs acting on CNS causing drug dependence.
2. **Iatrogenic Disease (Drug-Induced Disease):** Drug prescribed for a disease causes another disease, e.g. aspirin-induced asthma or peptic ulcer - antipsychotic-induced Parkinsonism.

PHARMACOGENETIC DISORDERS

These are genetic abnormalities that are revealed only by the effect of drugs.

Acetylation Polymorphism

- The population is divided into slow and rapid acetylators. Drugs metabolized by acetylation accumulate in the slow acetylators and produce toxic effects more than in the rapid acetylators. **Examples,** in slow acetylators:
  - a. Isoniazid → neuropathy and hepatitis.
  - b. Procainamide → systemic lupus erythematosis (SLE).

Hemolytic Anemia due to G6PD Deficiency

- Congenital deficiency of glucose-6-phosphate dehydrogenase (G6PD) enzyme renders RBCs readily hemolyzed in presence of some oxidant drugs as antimalarials, sulfonamides and fava beans (favism).

Porphyrias

- Genetic disorders of porphyrin metabolism → ↑ levels of porphyrins and their precursors → severe neurological disturbances & may cause death.
- Barbiturates and sulfonamides precipitate porphyria by increasing ALA-synthetase activity with accumulation of porphyrin precursors.

Succinylcholine Apnea

- Succinyl choline may cause respiratory muscle paralysis with apnea in genetically predisposed patients due to failure of its breakdown due to genetic defect in pseudocholine esterase responsible for its breakdown.

Malignant Hyperthermia

- Genetic disorder in which skeletal muscles fail to sequester Ca^{++} in sarcoplasmic reticulum following administration of succinylcholine and halothane. This results in marked muscle rigidity & rise of body temperature.

Steroid-Induced Raised Intraocular Pressure

- Occurs in genetically predisposed individuals receiving corticosteroids.

Genetic resistance to anticoagulants

- Hereditary ↑ in vitamin K reactivation → Resistance to anticoagulants (e.g., warfarin) which inhibit synthesis of vitamin K -dependent clotting factors through inhibition of vitamin K reactivation.

DRUG ALLERGY

- Allergic reactions are adverse effects mediated by immunogenic mechanisms.
- Most drugs are simple chemicals acting as incomplete antigens or haptens.
- Drug allergy is dose-independent and occurs in minority of patients.
- Cross-allergy may occur within a group of chemically related drugs.
- Chief target organs are skin, respiratory tract, GIT, blood & blood vessels.

Type I Reaction (immediate type; anaphylactic):

- IgE-mediated: antigen antibody reaction on surface of blood basophils or tissue mast cells. e.g., asthma, anaphylaxis, angioedema (with penicillins).

Type II Reaction

- IgG or IgM antibodies are fixed to a circulating blood cell → complement-dependent lysis. e.g., hemolytic anemia (with methyldopa), systemic lupus (with procainamide) & agranulocytosis (with chloramphenicol).

Type III Reaction

- Antigen antibody (IgG) complex is deposited in capillary beds → serum sickness syndrome & glomerulonephritis (with sulfonamides and penicillin).

Type IV Reactions (Delayed type; cell-mediated)

- Antigen stimulates T-cells to release lymphokines.
- It is involved in allergic contact dermatitis from topically applied drugs.

Diagnosis of Drug Allergy

1. History and type of reaction.
2. Intradermal and conjunctival tests.

Measures against Allergy

Treatment: epinephrine - hydrocortisone - antihistamines.

Prophylaxis:

1. Cromolyn (inhibits histamine release)
2. Anti-IgE monoclonal antibodies.
3. Desensitization or hyposensitization.

DRUG INTERACTIONS

- Drug interactions occur when one drug modifies the action of another drug in the body. Clinically important drug interactions occur with:

1. Drugs that possess:

a. A steep dose-response curve.
b. Low therapeutic index (TI).
c. Enzyme inducing or inhibiting properties.
d. Zero-order & saturable kinetics.

2. Patients:

a. Receiving multiple drugs.
b. Severely ill - impaired liver or kidney function.
c. At extremes of age

Important Examples

- Oral anticoagulants.
- Oral hypoglycemics
- Cardiac glycosides.
- Antiepileptics.

Types of Drug Interactions

- **Pharmaceutical** incompatibilities occur outside the body e.g., precipitation when drugs are mixed in solution for IV administration
- **Pharmacokinetic;** involving absorption, distribution, metabolism & excretion.
- **Pharmacodynamic**: interactions at the sites of action or nearby.

I. Pharmacokinetic Interactions

A. Interactions at site of absorption

- Tetracyclines chelate metals → ↓ absorption of Ca^{2+}, Mg^{2+}, & Al^{3+}containing antacids.
- Drugs that alter GI motility influence the rate and extent of absorption of other drugs (e.g., anticholinergics & prokinetic drugs).
- Drugs that change the pH of the gut contents can also affect the rate of absorption of other drugs by affecting drug ionization.

B. Competition for plasma protein binding sites

- A drug with higher affinity will displace another drug with less affinity increasing its free concentration and hence its effect.
- Clinically important protein binding interactions necessitate that the drug should have a relatively small V_d so that most of drug is in the circulation & more than 90% of the drug is plasma-protein-bound so that small displacement of bound form → large increase in percentage of free form.

Examples of displacement interactions

- Aspirin displaces warfarin → bleeding.
- Sulfonamides & vitamin K displace bilirubin → hyperbilirubinemia → kernicterus in the newborn.

C. Interactions involving metabolism

1. Enzyme Induction by enzyme inducers→

- ↑ Metabolism of drugs given simultaneously → ↓ level→ ↓effect
  - **Rifampicin** →↑ metabolism of oral contraceptives → pregnancy.
  - **Phenytoin** →↑ metabolism of vitamin D → osteomalacia.

2. Enzyme inhibition by enzyme inhibitors→

- ↓ Metabolism of drugs given simultaneously→ ↑ level → potentiation
  - **Erythromycin** inhibits metabolism of theophylline.
  - **Ciprofloxacin** inhibits metabolism of theophylline, warfarin.

D. Interactions at Site of Excretion

- Alkalization of urine→↑ionization of acidic drugs (aspirin) →↓tubular reabsorption →↑ excretion (useful in treatment of toxicity)
- Acidification of urine →↑ionization of basic drugs (amphetamines) →↓tubular reabsorption →↑ excretion (useful in treatment of toxicity.
- Probenecid competes with penicillin for renal tubular excretion → inhibits its excretion →prolongs its action.

II. Pharmacodynamic Interactions

A. Enhancement Interactions

- **Summation** (1+1= 2) i.e. additive effect. Example: Additive analgesic effect of paracetamol + codeine.
- **Synergism**[19] (1+1= 5): when two drugs work together. Example: sulfonamides plus trimethoprim act synergistically to block two sequential steps in bacterial folic acid metabolism.
- **Potentiation** (a +b= B): occurs when two drugs are taken together and one of them (having no effect on its own) intensifies the action of the other. Example: beta lactamase inhibitor (has no antibacterial effect) intensifies the antibacterial effect of beta lactamase sensitive penicillins.

B. Antagonistic Interactions (1+1=0)

- β Blockers or α blockers with their agonists.

Beneficial Drug Interactions

- By combining drugs having different mechanisms of action or drugs that correct undesirable reactions of each other.
- Examples: multiple drug therapy for treatment of hypertension, heart failure.

Categorization of drug interactions

- There are various systems for categorization of drug interactions. The following is an example.

Category A:

- No known interaction

Category B:

- Drugs may interact but no evidence of clinical concern.
- No action needed.

---

[19] The word synergism comes from two Greek words: erg meaning "to work", and syn meaning "together"; hence, synergism is a "working together".

Category C:

- Drugs may interact with each other in a clinically significant manner.
- The benefits of concomitant use usually outweigh the risks.
- Monitor Therapy. Dosage adjustments may be needed.

Category D:

- Drugs may interact with each other in a clinically significant manner.
- A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks.
- Consider Therapy Modification: aggressive monitoring, empiric dosage changes, choosing alternative agents.

Category X:

- Drugs may interact with each other in a clinically significant manner.
- The risks associated with concomitant use of these agents usually outweigh the benefits.
- These agents are generally considered contraindicated. Avoid Combination.

Prescription Writing
&
Dispensing Medication

I. Self-medication (OTC agents):

- OTC (Over-the-counter) agents are drugs dispensed without a prescription as they have a high safety margin e.g. simple analgesics, antacids, laxatives, antihistaminics, antitussives & expectorants & nasal & oral decongestants.

  Risks associated with the use of OTC drugs:

  1. May aggravate preexisting disease e.g. nasal decongestant in hypertensives.
  2. May cause drug interactions e.g. aspirin →bleeding in patients on warfarin.
  3. May lead to complications e.g. peptic ulcer with NSAIDs and electrolyte disturbances with laxatives in the elderly.

II. Behind the counter drugs (BTC)

- Drugs that can be prescribed by pharmacist without consulting the physician.

III. Prescription-only medicines (PoM)

- Drugs that can not be dispensed without a prescription. In Egypt, there are 3 types of prescriptions:
  1. **Ordinary prescription:** used for drugs requiring prescription by specialists e.g. digoxin
  2. **Special prescription:** used for some drugs with low addiction liability e.g. sedative hypnotics. These drugs are called "table II drugs".
  3. **Narcotic prescription:** for highly addictive drugs e.g. morphine. Prescription forms are supplied by local health authorities. The physician writes 2 forms of prescription (one is kept by pharmacist to be dispensed only once within 5 days from its date). Dose is written both numerically & alphabetically & the patient's & doctor's identities are included.
  4. **e-prescription:** electronic prescription; on the internet, permiting conferencing between the physician, the pharmacist and the patient.

Patient Noncompliance

- Patients do not accurately follow physician's instructions in taking medication resulting in under- or over-utilization of the prescribed drug.

Causes of noncompliance

- **Disease cause:** e.g. psychiatric & chronic diseases especially with minor symptoms (hypertension…), extremes of age and lonely patients.
- **Drug causes: e.g.** unpleasant taste or odor, undesirable route (injection, rectal...) or complex regimen (multiple drugs, complicated instructions).
- **Doctor causes**: inadequate physician-patient relationship & lack of supervision.

Categories of Teratogenic Risk

Category A: Controlled studies failed to prove risk (e.g. vaginal nystatin)

Category B: No adverse effects in animals, but no controlled studies on pregnant women to ensure risk (e.g. amoxicillin, azithromycin)

Category C: Studies in animals are suggestive but no controlled studies on pregnant women (e.g. co-trimoxazole, ciprofloxacin)

Category D: Evidence of fetal adverse effects, but the benefits outweigh the risks (*e.g.* tetracyclines, sulfonamides when near term 'due to increased toxicity to the new-born')

Category X: Proven fetal risks outweigh any possible benefit.

Autonomic Pharmacology

Intended Learning Outcomes (ILOs)

By the end of this chapter, the student will be able to:

- Discuss key biochemical and cellular events that take place in cholinergic and adrenergic nerve terminals and at target organ junctions upon stimulation.
- Summarize the points of potential pharmacological intervention in the synthetic, storage, release, receptor binding and termination steps of the neurotransmitters acetylcholine and norepinephrine and of the neurohormone epinephrine.
- Discuss the subtypes of the adrenergic and cholinergic receptors including their major peripheral locations and the major target organ responses to receptor stimulation.
- Identify prototype drugs that act to mimic, stimulate or block the: synthesis, storage, release, receptor binding, or removal of acetylcholine, norepinephrine at nerve terminals.
- Attribute the clinical use of different agonists or antagonists to their effects on different autonomic receptors.
- Identify the physiological and pathogenic role of various autacoids (histamine , serotonin, eicosanoids, angiotensin and kinins). Summarize the points of potential pharmacological intervention in the synthetic, storage, release and receptor binding of such autacoids.
- Discuss the development of various synthetic analogus for endogenous autacoids.

ADRENERGIC PHARMACOLOGY

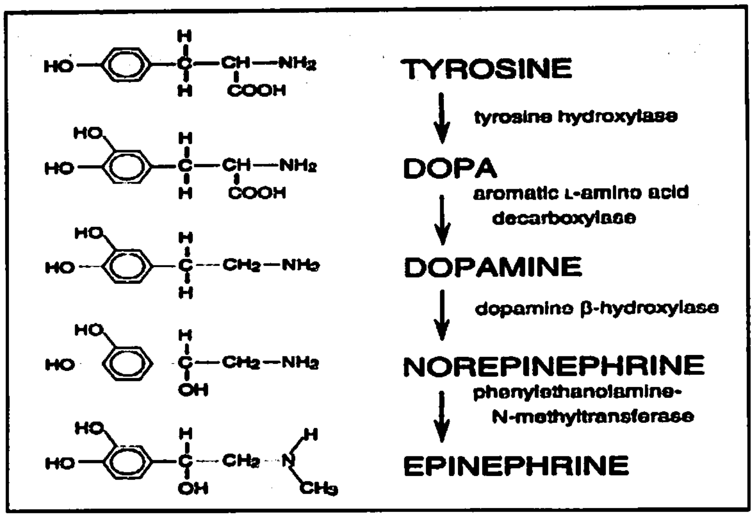
- The sympathetic system is an important regulator of activities of the heart & peripheral vasculature especially in response to stress.
- Adrenergic neurotransmitters are responsible for transmission at all postganglionic sympathetic neurons, except those of sweat glands.

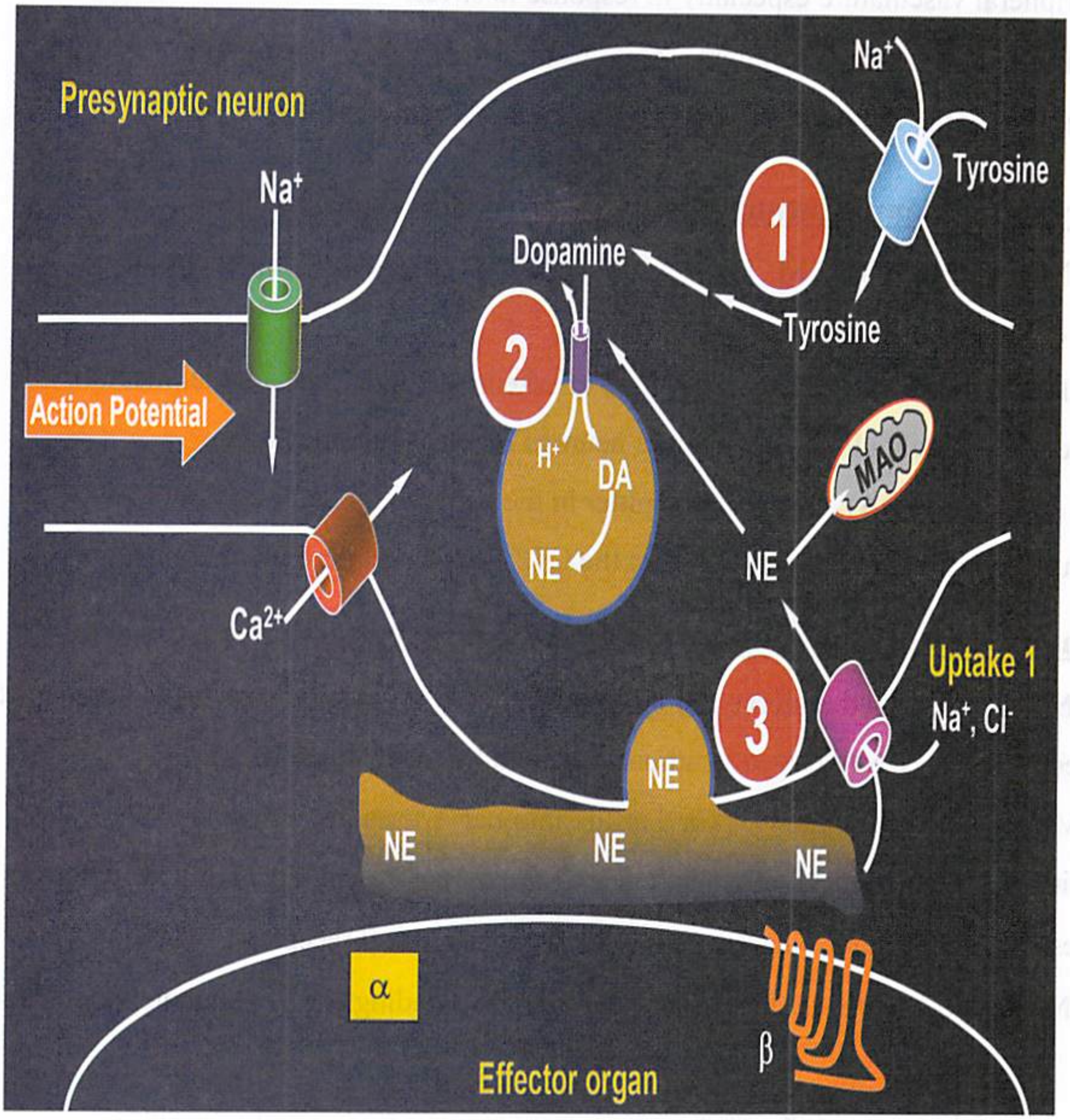
Adrenergic Neurotransmitters (endogenous catecholamines)

1. **Norepinephrine (NE)**: The transmitter of postganglionic sympathetic fibers & of certain tracts in the CNS.
2. **Epinephrine (Epi)**: major hormone of adrenal medulla. The adrenal medulla receives preganglionic cholinergic neurons & releases epinephrine.
3. **Dopamine (DA)**: Central transmitter in the extrapyramidal, mesolimbic & tubero-infundibular pathways & in the CTZ. It is also a peripheral transmitter.

Synthesis, storage & release of adrenergic transmitters

- NE is synthesized in nerve cell (see fig) & stored in synaptic vesicles of adrenergic neurons. Epi is synthesized in adrenal medulla by methylation of NE.
- Membrane depolarizion → Ca^{2+} influx into nerve terminal →fusion of vesicle with presynaptic membrane (partial exocytosis) → discharge of NE & other vesicle contents into synaptic cleft→NE activates α & β receptors.
- NE effect is terminated by re- uptake into nerve endings or by metabolic degradation.


TYROSINE
tyrosine hydroxylase
DOPA
aromatic L-amino acid decarboxylase
DOPAMINE
dopamine β-hydroxylase
NOREPINEPHRINE
phenylethanolamine-N-methyltransferase
EPINEPHRINE


Presynaptic neuron
Na⁺
Action Potential
Ca²⁺
Dopamine
2
H⁺
DA
NE
1
Na⁺
Tyrosine
Tyrosine
MAO
NE
Uptake 1
Na⁺, Cl⁻
3
NE
NE
NE
NE
α
β
Effector organ

Adrenergic Neuron

Synthesis, Release & Fate of NE

Drugs Affecting NE Release[1]

- NE release is controlled centrally by nucleus tractus solitarus (NTS)[2] & peripherally by homotropic (transmitter affects its own release) & heterotropic (transmitter affects release of another transmitter)[3] regulation by presynaptic neurons.

↑ Release

- Activation of central/ presynaptic β receptors.
- Tyramine
- Amphetamine
- Ephedrine.
- Nicotine (heterotropic;Nn)

↓ Release

- Activation of central/ presynaptic α_2 receptors→ negative feedback by excess NE (homotropic).
- ACh (heterotropic; M_2).
- Clonidine.
- Methyldopa

} **α_2 agonists**

Fate of catecholamines

I. Uptake

A. Uptake 1 (amine pump): actively transports NE from synaptic cleft into neuronal cytoplasm to be stored in granules or metabolized by MAO enzyme (the main fate of released NE).

- **Blocked by:** tricyclic antidepressants (TCA) - cocaine.

B. Vesicular: from neuronal cytoplasm to storage vesicles for re-use.

- **Blocked by:** reserpine (depletes stores).

C. Uptake II: to target organs for metabolism

- **Blocked by:** glucocorticoids.

---

[1] Tyramine, amphetamine & ephedrine release NE from adrenergic neuron. Reserpine depletes NE stores & guanethidine inhibits NE release (adrenergic neuronal blockers).

[2] Clonidine & methyldopa act on central α_2 receptors in NTS→↓ sympathetic discharge.

[3] Release of NE & Epi from adrenergic nerves & adrenal medulla by nicotine acting on Nn presynaptic receptors →↑ BP in smokers.

II. Enzymatic Degradation of catecholamines

- The monoamines, epinephrine, NE & DA are catecholamines (contain catechol nucleus[4]). They are degraded **mainly** by oxidative deamination by monoamine oxidase (MAO) & to a lesser extent by methylation by catechol-o-methyl transferase (COMT).
- The end product; vanilylmandelic acid (VMA) is excreted in urine → ↑ in pheochromocytoma (used in diagnosis).
- MAO inhibitors are used in depression & parkinsonism.
- COMT inhibitors are used in parkinsonism.

Classification of Adrenergic Receptors

I. Alpha adrenergic receptors

A. Alpha$_1$ (stimulatory except on GIT & urinary walls)

1. Vasoconstriction
2. Relaxation of walls of GIT & urinary tracts.
3. Contraction of GIT & urinary sphincters.
4. Contraction of prostate & vas deferens.
5. Stimulate dilator pupillae → active mydriasis.
6. Liver glycogenolysis & K^+ release.

Coupled to G_q → ⊕ PLC → ↑IP_3 (↑Ca^{2+}) & DAG (⊕ PKC)

B. Postsynaptic alpha$_2$ (inhibitory except in platelets & blood vessels)

1. ↓ Central sympathetic outflow → ↓ BP.
2. Inhibit lipolysis.
3. Inhibit insulin secretion (predominant).
4. Inhibit renin release.
5. Stimulate platelet aggregation & vasoconstriction.

Coupled to G_i → ⊖ adenylyl cyclase → ↓ cAMP → ⊖PKA

C. Presynaptic alpha$_2$

1. Inhibit NE release from sympathetic nerves.
2. ↓ Ach release in the heart & intestine.

---

[4] Catechol nucleus is a benzene ring with 2 OH groups.

II. Beta-adrenergic receptors

A. Beta$_1$ (excitatory)

1. Cardiac stimulation.
2. Lipolysis → ↑ plasma FFA (β_1 and β_3).
3. ↑Renin secretion.

- Coupled to G_s protein→⊕ adenylyl cyclase →↑c-AMP→ ⊕PKA

B. Beta$_2$ (inhibitory to smooth muscles)

1. Bronchodilation & mast cell stabilization.
2. Vasodilation of skeletal & coronary blood vessels.
3. Uterine and intestinal relaxation.
4. Stimulate insulin release (weak effect).
5. Liver & muscle glycogenolysis & k^+ uptake.
6. Skeletal muscle tremors

III. Dopaminergic receptors

D$_1$: vasodilation of renal, coronary, cerebral & mesenteric blood vessels.

D$_2$: **Postsynaptic**: central in the extrapyramidal, tuberoinfundibular, & mesolimbic pathways & in the CTZ.

Presynaptic: ↓ DA & NE release from nerve endings.

Sympathomimetic Drugs

Classification According to Chemical Structure

Catecholamines: NE- epinephrine- isoprenaline –DA- dobutamine ……

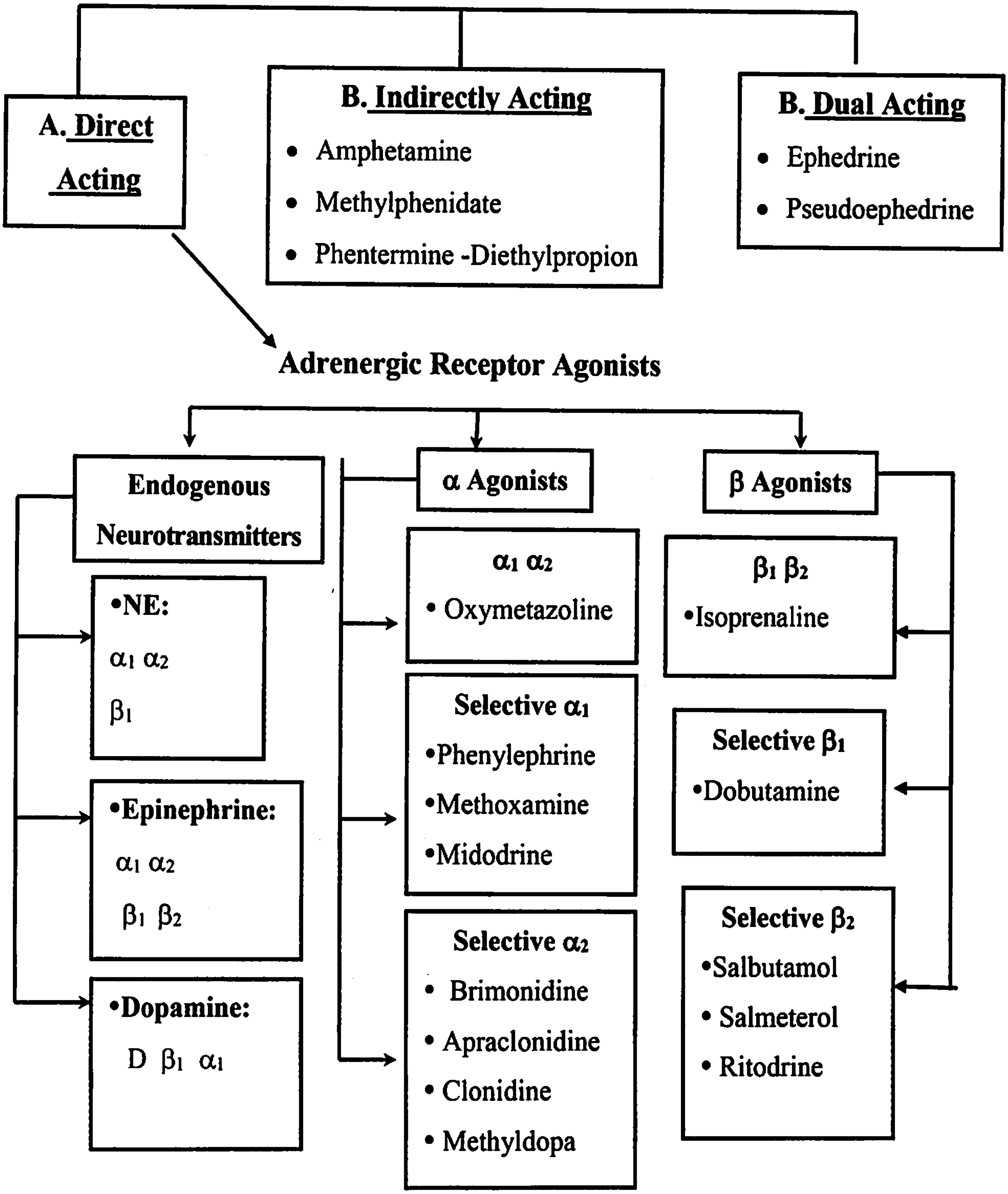
- Contain catechol nucleus which is a benzene ring with 2 OH groups.
- Destroyed by MAO & COMT enzymes: cannot be given orally -shorter acting.
- Polar compounds:do not readily enter CNS (but exhibit some CNS effects).

Non Catecholamines: ephedrine, amphetamine, ……..

- Not destroyed by MAO &COMT: can be given orally -longer acting.
- Readily enter CNS: strong CNS effects.

Sympathomimetic Drugs

Classification According to Mechanism of Action



A. Direct Acting

B. Indirectly Acting
- Amphetamine
- Methylphenidate
- Phentermine -Diethylpropion

B. Dual Acting
- Ephedrine
- Pseudoephedrine

Adrenergic Receptor Agonists

Endogenous Neurotransmitters
- **NE:** α_1 α_2 β_1
- **Epinephrine:** α_1 α_2 β_1 β_2
- **Dopamine:** D β_1 α_1

α Agonists

α_1 α_2
- Oxymetazoline

Selective α_1
- Phenylephrine
- Methoxamine
- Midodrine

Selective α_2
- Brimonidine
- Apraclonidine
- Clonidine
- Methyldopa

β Agonists

β_1 β_2
- Isoprenaline

Selective β_1
- Dobutamine

Selective β_2
- Salbutamol
- Salmeterol
- Ritodrine

N.B.:
- DA agonists: DA– dopexamine (D_1 D_2 B_2) – fenoldopam (D_1) – bromocriptine (D_2).
- Selective α_2- agonists are sympatholytics as they ↓ NE release.

DIRECTLY ACTING SYMPATHOMIMETICS

Epinephrine

Pharmacological actions

I. Cardiovascular System

A. Heart (β_1)

- ↑Force of contraction (positive inotropic).
- ↑ Heart rate (positive chronotropic).
- ↑ Conduction velocity (positive dromotropic).
- Enhances automaticity and causes arrhythmias.

B. Blood vessels

- VC of arterioles of skin, mucosa, splanchnic & renal vessels (α_1).
- VC of veins (α_1).
- Vasodilatation of skeletal & coronary vessels (β_2 effect).

C. Effects on Blood Pressure

- ↑ Systolic : vc (α_1) & chronotropic & inotropic effects (β_1 mainly).
- ↑Diastolic: α_1,VC (may ↓ with very low doses due to β_2 VD of skeletal bv)
- ↑ Mean BP (no reflex bradycardia as it is antagonized by chronotropic & inotropic β effects).
- ↑ Pulse pressure.

Epinephrine Reversal in Animals

- Hypotensive effect of epinephrine (β_2-mediated VD of skeletal vessels) is masked by its α_1 hypertensive effect. **After α-blockade, β_2-mediated hypotensive effect is unmasked.**

II. Respiratory System:

- Bronchodilatation (β_2 action).
- Decongestion of BVs of mucous membrane of upper respiratory tract (α_1).

III. Eye

- Contraction of dilator pupillae (α_1) → active mydriasis without cycloplegia.
- ↓ IOP by decreasing aqueous humor formation.

IV. Effect on other smooth muscles

- Relaxation of GIT wall (β, α); α_2 agonists → ↓ presynaptic Ach release.
- Contraction of sphincters of GIT & urinary tracts (α_1).
- Inhibition of uterine tone & contractions in last months of pregnancy (β_2).

V. Metabolic actions

- Hepatic glycogenolysis → β_2 (mainly) & α_1.
- Insulin release → inhibited by α_2 (dominant) & stimulated by β_2.
- Lipolysis (β_1 & β_3) & inhibited by α_2.
- Renin release (β_1) → ↓ serum K^+ (also decreased by↑ hepatic uptake; β_2)

VI. Skeletal muscle: tremors → β_2 & central.

Therapeutic Uses

1. Anaphylactic shock (reverses bronchospasm & hypotension → life saving).
2. Asthma if associated with locked lung.
3. Cardiac Arrest.
4. Arrests bleeding (topical hemostatic →VC, e.g. in epistaxis).
5. Added to local Anesthetics to prolong their action.
6. Open Angle glaucoma (↓ IOP): dipivefrine (pro-epinephrine) is used instead of epinephrine (since epinephrine is destroyed in alkaline medium).

Preparations and Dosage

- SC or IM **1:1,000** in mild anaphylactic shock.
- IV **1:10,000**: severe anaphylactic shock - cardiac arrest (or intra-cardiac).
- Inhalation **1:100** in asthma.
- Topical: **1:100** in bleeding states - **1%** solution for ophthalmic use.

Norepinephrine (noradrenaline)

- Natural catecholamine
- Acts on α & β_1 receptors as epinephrine (minimal effect on β2 receptors).
- α effect → marked vasoconstriction →↑ BP or gangrene.
- β_1 effect → positive inotropic & chronotropic effect.
- Marked ↑↑ BP → reflex vagal bradycardia which overcomes its direct positive chronotropic effect.
- If atropine is given before norepinephrine, it will block the reflex vagal bradycardia, then the direct positive chronotropic effect of norepinephrine (tachycardia) will be apparent.
- **Used in shock**:

  - Septic shock

  - Cardiogenic shock (if BP < 70mmHg).

  - Shock after resection of pheochromocytoma.

  - Shock with pulmonary embolism.

Isoproterenol (isoprenaline)

- Synthetic catecholamine.
- Very potent β-receptor agonist (with little effect on α receptors).
- β_1 effect → +ve chronotropic & inotropic → marked ↑ in cardiac output.
- β_2 effect → vasodilation →↓ diastolic & mean BP→ reflex ↑ in HR.
- **Used in**:

  - Bradycardia 2^{ry} to heart block (rarely).

- Marked ↑↑ in HR → anginal attack & sudden death.

Dopamine & Dobutamine: see below.

Comparison between Dopamine and Dobutamine

Dopamine (D, β_1, α_1)	Dobutamine (β_1)
• Natural catecholamine.	• Synthetic catecholamine.
• **D_1-agonist** (at low dose): - VD of several vascular beds, e.g., renal blood vessels resulting in increased renal blood flow. - Headache, nausea, vomiting.	• No D_1 agonist effect.
• **β_1-agonist** (at moderate dose): -Cardiac stimulation (+ve inotrope & chronotrope) - Anginal pain and arrhythmia.	• **β1-agonist**: - Cardiac stimulation: inotropic > chronotropic. - Less arrhythmogenic.
• **α_1-agonist** (at high dose): - VC (including renal): hypertension, gangrene	• No α_1-agonist effect.
Uses 1. Acute HF & cardiogenic shock: • DA is preferred in cases with hypotension (α →↑ BP) or renal impairment (D_1 → renal VD). 2. Chronic refractory HF (short term treatment).	**Uses** • Similar to DA but preferred in normotensives (no α effect) with preserved renal function (no D_1 renal VD effect).
Administration (IV infusion titrated gradually) • Dose range: 2 μg/kg/min→20 μg/kg/min	**Administration:** Similar to DA • Dose range: 2.5μg/kg/min→20 μg/kg/min

Adverse effects

(Avoided by gradual titration of infusion)

1. Palpitation- anginal pain-arrhythmia (less with dobutamine).
2. Hypertension & gangrene (with dopamine).
3. Headache, nausea, vomiting (with dopamine).

Dopexamine

- A dopamine analogue that activates β_2 besides D_1 & D_2 receptors.
- Very weak positive inotropic but powerful splanchnic vasodilator → ↓ afterload & improves blood flow to vital organs, including the kidney.
- Useful in shock following myocardial infarction, trauma, open heart surgery in those with low cardiac output & peripheral vasoconstriction.

Fenoldopam

- D_1 receptor agonist → peripheral VD in some vascular beds.
- It is used mainly IV for the treatment of severe hypertension.

Selective β_2 agonists

Advantages over nonselective β agonists

1. No cardiac complications in regular doses.
2. Longer acting (not metabolized by MAO or COMT).
3. May be given by many routes (oral, inhalation, parentral).

Therapeutic uses

1. Bronchial asthma: salbutamol/albuterol; short acting
   salmeterol; long acting
2. Prevent premature labor & threatened abortion (terbutaline & ritodrine).

Adverse effects (less with inhalation therapy):

1. Anxiety, restlessness and headache.
2. Tremors of skeletal muscle.
3. Tachycardia (at high concentration they stimulate β_1 receptors).
4. Tolerance on long term systemic use (β receptor downregulation).
5. Hypokalemia and muscle cramps.
6. Hypoxemia: (β_2 effect→ VD > bronchodilation → ↓ blood oxygenation).

Selective α_1 agonists

1. Phenylephrine

- An α_1 agonist.
- Longer acting than CA (not a CA→ not inactivated by COMT).

Uses:

a. Mydriatic for fundus examination (no cycloplegia; preferred to atropine substitutes especially in patients with glaucoma).

b. Eye & nasal decongestant.

c. Hypotensive states to ↑ BP.

d. Paroxysmal supraventricular tachycardia associated with marked hypotension (↑ BP→ reflex vagal stimulation).

e. Local treatment for hemorrhoids.

2. Methoxamine

- α_1 agonist that acts like phenylephrine.
- It may induce prolonged ↑ in BP due to vasoconstriction.
- **Uses**: hypotensive states (parenteral).

3. Midodrine

- A prodrug that is hydrolyzed to desglymidodrine (α_1 agonist).
- **Uses**: postural hypotension (mainly).

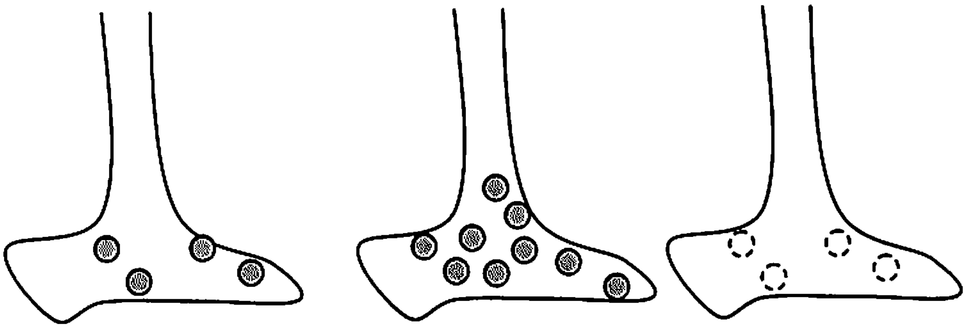
Adverse effects of α- agonists

1. Hypertension & bradycardia.
2. Rebound nasal congestion & atrophic rhinitis (with local application).

INDIRECTLY ACTING SYMPATHOMIMETICS

General features:

1. Act mainly by NE release; once NE stores are depleted→tolerance & tachyphylaxis.
2. They are non-catecholamines; so
   - Not destroyed by MAO in the GIT → **Can be given orally**
   - Not metabolized by neuronal MAO → **Longer duration of action**
   - Can penetrate the BBB → **Act on the CNS**
3. They can lead to **drug interactions** with
   - **a. MAOIs:** serious hypertensive crisis (cheese reaction) may occur since nerve endings of patients on MAOIs are studded with NE.
   - **b. Reserpine:** lose their effect as reserpinized nerves do not contain NE.



Normal nerve ending

Nerve ending under MAOIs treatment

Nerve ending under reserpine treatment

Members:

I. Amphetamine

II. CNS Stimulants e.g.[5]

- Methylphenidate - dextroamphetamine - methamphetamine.

III. Anorexigens for treatment of obesity e.g.[6]

- Phentermine -diethylpropion

---

[5] Other CNS stimulants: Atomoxetine (NE reuptake inhibitor used in Attention Deficit Hyperkinetic Disorders; ADHD); does not induce addiction.

[6] Other anorexigens: Benzphetamine & phendimetrazine.

Mechanism of action

- They act mainly by stimulating the release of NE & to a lesser extent by inhibiting its uptake by adrenergic neurones.

CNS actions:

1. Strong CNS stimulation (penetrate BBB more than ephedrine)
2. Strong anorexigenic

Uses:

1. Narcolepsy[7].
2. Attention Deficit Hyperkinetic Disorders of Childhood (ADHD).
3. Obesity: short term treatment with phentermine & diethylpropion (low abuse potential). Amphetamine is not used for fear of dependence.

Adverse Effects:

1. Marked CNS stimulation →hallucination, psychosis, convulsions & dependence on prolonged use [8].
2. Marked CVS stimulation → palpitation, arrhythmia, hypertension.
3. Marked Anorexia.
4. New anorexigens → 1^{ry} pulmonary hypertension & valvular heart diseases.

Tyramine (decarboxylated tyrosine)

- Indirectly acting sympathomimetic → releases CA.
- High conc. in fermented foods (cheese, beer, fava beans, chicken liver).
- Metabolized by MAO in GIT, inactive orally due to a high I^{st} -pass effect.

Cheese reaction:

- Patients on MAOIs should avoid tyramine-rich food (e.g. old cheese) since tyramine will escape metabolism & reach systemic circulation → NE release from neurons, studded with NE (due to MAOIs) → hypertensive crisis.

---

[7] **Modafinil**: non-amphetamine for narcolepsy (↑DA signaling or activity of wake-promoting histamine neurons in tubero-mammillary nucleus.

[8] Amphetamine does not lead to dependence in narcolepsy or ADHD (unexplained reasons).

Mixed- or Dual-acting Sympathomimetic Drugs

Members:

- Ephedrine
- Related compounds: pseudoephedrine

Mechanism of action

- They are dual acting sympathomimetic i.e. they act both by release of NE (similar to amphetamine but are much less potent) with some direct action on the receptors (i.e. similar to epinephrine but are also much less potent).

CNS actions

- Mild CNS stimulation & anorexia as compared to amphetamine.

Uses

1. Epistaxis: topical ephedrine.
2. Oral nasal decongestants[9]: pseudoephedrine.
3. Spinal shock: ephedrine IMI (releases NE from anaesthetized sympathetic nerves).
4. Nocturnal enuresis (in children).
5. Urine incontinence (in adults).

Adverse Effects

1. Minimal CNS stimulation → insomnia, anxiety.
2. Minimal CVS stimulation → palpitation, hypertension.
3. Urinary retention.
3. Paradoxically, may induce sleepiness in children!!

---

[9] Indirect-acting sympathomimetics are preferred to the direct-acting phenylephrine (unpredictable absorption). Many oral OTC medications contain pseudoephedrine, least CNS effects.

Choice of Sympathomimetic Drugs

I. Cardiostimulants (β_1 mainly)

- Chronic refractory HF - acute HF & cardiogenic shock after AMI or open heart surgery: DA (β_1 & D_1; renal VD) & dobutamine.
- Anaphylactic shock: epinephrine (α_1,VC; β_1, ↑ COP; β_2, bronchodilation).
- Heart block (isoprenaline) or cardiac arrest (intracardiac epinephrine).

2. Vaspressors (α)

- Hypotensive states requiring peripheral VC as septic shock, spinal shock & after sympathectomy (NE, ephedrine, phenylephrine).
- Chronic orthostatic hypotension (midodrine).
- PSVT with marked ↓ in BP (phenylepherine → ↑BP → vagal stimulation).

3. Local vasoconstrictors (α)

- To prolong the duration of local anesthetics (epinephrine).
- Hemostatics e.g., in epistaxis (ephedrine, epinephrine).
- Nasal decongestants (oxymetazoline, phenylepherine).

4. Systemic nasal decongestants[10] (α)

- Allergic rhinitis & sinusitis (pseudoephedrine, phenylepherine)

5. Ophthalmic applications (α)

- Mydriatic for fundus examination (phenylephrine)
- Conjunctival decongestant in allergy (phenylephrine, oxymetazoline)
- Simple glaucoma (apraclonidine, brimonidine, dipivefrine)

6. Bronchodilators (β_2): asthma (β_2 agonists e.g. salbutamol - salmeterol).

7. Tocolytics (β_2): premature labor - threatened abortion (terbutaline & ritodrine).

8. CNS stimulants: narcolepsy- ADHD of children (amphetamine, methylphenidate).

9. Appetite suppressants: obesity (phentermine -diethylpropion).

---

[10] α-agonists e.g. oxymetazoline are preferred as local nasal decongestant (more VC); indirect agents e.g. pseudoephedrine are preferred as systemic nasal decongestant (longer acting).

Beta Adrenoceptor Blockers (βBs)

- βBs are competitive antagonists of catecholamines at β-adrenoceptors.

Pharmacological actions of βBs

A. Cardiovascular Actions

1. **Anti-anginal effect**: improve imbalance between O_2 supply & demand

A. ↓ O_2 demand:

- ↓ HR & myocardial contractility.
- ↓ BP.
- Inhibit lipolysis→↓ fatty acid utilization.

B. ↑ O_2 supply:

- ↑ coronary filling during diastole (by ↓ HR → ↑ diastolic period).
- Redistribution of coronary flow to sub-endocardial area.

2. **Anti-arrhythmic effect**

- Block intrinsic sympathetic activity in slow fibres:

- ↓ V_{max} and delay conduction→↓ SAN rate & AVN conduction.

-↓ Phase 4 slope → slow automaticity of sympathetic – induced ectopic focus.

3. **Anti-hypertensive effect**

- **β_1-blockade** (mainly)
  - Suppress renin release.
  - Negative inotropic & chronotropic effects.
- β_2 – blockade
  - Central sympatholytic effect (block presynaptic β_2 receptors in NTS).
  - Peripheral sympatholytic effect (block presynaptic β_2 receptors).
- Resetting of baroreceptors.
- Some β-blockers are vasodilators.

4. **Vasoconstriction (unopposed α actions)**

- In ciliary vessels→↓ aqueous humor production → ↓ IOP.
- In mesenteric vessels →↓ hepatic blood flow (↓ drug metabolism).
- In skeletal muscles → ↓ blood flow during exercise→ ↓work capacity.

B. Noncardiovascular Actions

1. Respiratory:

- Bronchoconstriction.
- Inhibit CA induced mast cell stabilization.

2. Metabolic

- Inhibit CA-induced glycogenolysis→ delay recovery from hypoglycemia.
- ↓ Insulin release→ glucose intolerance (not important if patient is on antidabetics).
- ↑ Plasma TG[11] : ↑ VLDL - ↓ HDL - ↓ HDL/LDL ratio[12].
- ↑ Plasma K^+ during exercise (inhibit uptake by liver).
- Inhibit conversion of T4 → T3.

3. CNS

- CNS depression (lipophilic βBs).
- Anxiolytics.

Therapeutic Uses

- Mainly in hypertension, ischemic heart disease and cardiac arrhythmias.

I. 2^{ry} to β_1 blockade

1. **Hypertension.**
2. **Ischemic heart disease**:
   - i. Angina pectoris, except vasospastic angina (may increase vasospasm).
   - ii. M. infarction (prophylactic & acute phase→ ↓ infarct size & mortality[13]).
3. **Cardiac arrhythmias.**
4. Heart failure (systolic): low dose carvedilol, bisoprolol, metoprolol.
5. Hypertrophic obstructive cardiomyopathy: relax septum →↓ outflow resistance.
6. Hyperthyroidism & thyrotoxic crisis (propranolol):

   Cardio-protective (β_1) - ↓ anxiety & tremors -inhibit conversion of T_4 to T_3.

---

[11] Effect on TG is due to unopposed alpha action which inhibits lipoprotein lipase. That is why it is lacking in combined alpha & β Bs & with β Bs with ISA and less with cardio-selective β Bs because the presereved β 2 action opposes the alpha action on lipoprotein lipase.

[12] Effect on HDL/LDL ratio may be due to changes in insulin sensitivity.

[13] ↓ Infarct size by its anti-anginal & ↓mortality by its anti-arrhythmic effects.

II. 2^{ry} to β_2 blockade

- **a. Open-angle glaucoma** (timolol & betaxolol)
- **b. Prophylactic in oesophageal varices**: non-selective ßBs reduce portal blood flow by: splanchnic vasoconstriction (β_2 block) - ↓COP (β_1 block).
- **c. Prophylaxis of migraine** (propranolol & timolol)
  - i. ↓ NE release which triggers attack.
  - ii. Vasoconstriction of extra-cranial blood vessels.
- **d. Essential tremors.**

III. 2^{ry} to α blockade

- **a. Acute dissecting aortic aneurysm**: (labetalol; of choice)
  - Powerful antihypertensive (combined α & β)→↓dissection until surgery.
- **b. Pheochromocytoma** (labetalol; of choice)
  - If propranolol is used it should be preceded by an α- blocker to avoid marked ↑ BP due to unopposed α-action after β-blockade.

IV. 2^{ry} to CNS effects:

- **Localized social anxiety disorder** (mask symptoms during public performance).

Adverse effects, contraindications & precautions

A. Due to β1 blockade

- Bradycardia - heart block.
- Heart failure (may be precipitated with high dose).
- Hypotension (more severe with vasodilator βBs).

B. Due to β2 blockade

- Cold extremities, fatigue & claudications (CI in peripheral vascular disease & vasospastic angina).
- Bronchospasm (CI in asthma).
- Prolongation of insulin-induced hypoglycemia.
- Glucose intolerance.
- Hyperkalemia in susceptible patients (e.g. renal impairment & diabetes).

C. Other adverse effects

i. Hypertriglyceridemia (& glucose intolerance→ ↑risk of ischemic heart disease)

ii. CNS: nightmares & depression.

iii. Sudden withdrawal → rebound angina & arrhythmias in ischemic heart disease (due to up regulation of ß receptors; less severe with ßBs with ISA) → **gradual withdrawal is required to avoid rebound.**

iv. Sexual dysfunction

Pharmacokinetics of β-blockers

- βBs are classified pharmacokinetically into 3 groups: lipophilic, hydrophilic & balanced (properties in between those of lipophilic & hydrophilic).
- Esmolol is hydrophilic, yet it has a very short duration of action ($t_{1/2}$ 8 min) due to hydrolysis by plasma esterases.

	Lipophilic Propranolol- metoprolol Carvedilol	**Hydrophilic** Atenolol- Nadolol
Absorption	• Well absorbed.	• Irregularly absorbed.
First pass effect	• Extensive	• Less
Bioavailability	• Less	• More
Distribution	• More CNS penetration → more CNS side effects.	• Less CNS penetration → less CNS side effects.
Elimination	• Mainly hepatic → suitable in renal impairment.	• Mainly renal → suitable in hepatic impairment.
t½	• Short t½ → frequent administration.	• Long t½ (except esmolol) → once/ day administration.

Members of Different Generations of βBs

Propranolol

- Prototype beta blocker with the following characteristics:
  1. **Lipophilic:** short duration, CNS side effects & avoided in liver dysfunction, thus newer agents with low lipid solubility were developed.
  2. **Non-selective:** induces wide spread side effects thus newer generations were developed: e.g., cardio-selective βBs, vasodilator βBs, & βBs with intrinsic sympathomimetic activity (ISA).
  3. **Membrane stabilizing effect (MSA):** induces local anesthesia of cornea on topical application in glaucoma, thus replaced by βBs with no MSA e.g., timolol (nonselective) & betaxolol (selective).

Generations of βBs

- Different βBs are distinguished by relative selectivity for β_1 & β_2 receptors, differences in lipid solubility, intrinsic sympathomimetic activity (ISA), membrane-stabilizing activity (MSA) & vasodilator effects.

	Lipophilic	**Balanced**	**Hydrophilic**	**Advantages**
Non-selective βBs	• Propranolol (MSA)	• Pindolol (ISA)	• Nadolol (long acting)	**β B with ISA induce less:** • Bradycardia. • Bronchospasm • Vasospasm.
Selective β_1Bs	• Metoprolol	• Bisoprolol	• Atenolol • Esmolol	• Less bronchospasm. • Less delayed recovery from hypoglycemia. • Less risk of Raynaud's phenomenon.
Vasodilator βBs	• Carvedilol (nonselective β B plus α-blockade)	• Celiprolol ($\beta_1$blocker plus β_2 agonist)		• Carvedilol decreases mortality in heart failure.

Esmolol

- It is an ultra-short–acting β_1-selective adrenoceptor antagonist.
- Hydrophilic but has a short $t_{1/2}$ (8 min.) due to hydrolysis by plasma esterases.
- Used in: supraventricular arrhythmias & arrhythmias of thyrotoxicosis, perioperative hypertension, myocardial ischemia in acutely ill patients.

Vasodilator βBs

Labetalol

- Selective α_1 & non-selective βB (α/β ratio 1:3).
- Used in most hypertensive emergencies.
- Used in hypertension during pregnancy & labor (pre-eclampsia).

Carvedilol

- Nonselective βB & α_1-selective blocker → vasodilator βB.
- Beneficial in chronic heart failure (see CVS) →
  - i. ↓ Oxygen free radical→ antioxidant.
  - ii. Inhibits vascular smooth muscle mitogenesis[14]

Nebivolol

- Selective β_1B.
- Releases nitric oxide from vascular endothelial cells → VD→ used effectively in treatment of hypertension.
- Does not induce bradycardia→ not used in ischemic heart disease.
- Does not induce sexual dysfunction.

---

[14] Independent of adrenoceptor blockade.

Alpha Adrenoceptor Antagonists

Classification

Non-selective		Selective	
Irreversible **Long acting**	**Reversible** **Short acting**	**Alpha$_1$** **Selective**	**Alpha$_2$** **Selective**
Phenoxybenzamine $\alpha_1 > \alpha_2$	Phentolamine $\alpha_1 = \alpha_2$ Plus direct VD	• Prazosin • Doxazosin • Tamsulosin	• Yohimbine[15] • Mianserin[16]

Other α Blockers: labetalol- carvedilol- ergot alkaloids.

Pharmacological actions of selective α_1 blockers

I. Cardiovascular actions

1. Mixed vasodilators:
    a. Arteriodilators→↓ peripheral resistance→ ↓blood pressure.
    b. Venodilators→↓ venous return→ postural hypotension.
2. Tachycardia (less than nonselective agents): nonselective agents block presynaptic α_2 receptors→↑ NE release → stimulates cardiac β_1 receptors.
3. Chronic use → compensatory ↑ in blood volume (fluid retention).
4. Prevent the pressor effects of usual doses of alpha agonists & convert pressor response of epinephrine to a depressor effect (epinephrine reversal).

---

[15] Yohimbine: α_2-selective antagonist used as an aphrodisiac →↑NE release → stimulates ejaculation.

[16] Mianserin is an antidepressant that increase NE release centrally.

II. Other actions

- Block α receptor →decrease tone of bladder neck muscles & prostate →↓ resistance to urine flow→ used in urine retention due to benign prostatic hyperplasia (BPH).
- Relaxation of vas deferens→ inhibition of ejaculation.
- Miosis - nasal stuffiness.

Therapeutic uses of α blockers[17]

1. BPH: prazosin, doxazosin,, tamsulosin.
2. BPH with essential hypertension: prazosin (tolerance develops due to tachycardia & fluid retention).
3. Hypertension in pregnancy and labor (labetalol).
4. Most hypertensive emergencies (labetalol).
5. Pheochromocytoma:
   - **Medical treatment**: before surgery or if inoperable: phenoxybenzamine is preferred; irreversible blocker[18].
   - **Intra-operatively**: if excess catecholamines results in hypertensive emergency : (phentolamine + β B/ or labetalol alone).

Adverse Effects of α blockers

1. 1st dose postural hypotension[19]: ↓ by giving small dose (1 mg) at bed time.
2. Tachycardia (marked with non-selective agents).
3. Impaired ejaculation and sexual dysfunction.
4. Nasal congesion, flushing, headache.
5. Drowsiness and nausea.

---

[17] Other unlabeled uses of α blockers: Raynauds disease (prazosin, but CCBs preferred), extravasation of α agonists (phentolamine prevents vasoconstriction & dermal necrosis).

[18] Major use of phenoxybenzamine & phentolamine is pheochromocytoma (tumor of adrenal medulla; releases Epi & NE →intermittent or sustained hypertension, headaches, palpitations ↑sweating.

[19] With syncope, seen ½–1 hour after 1st dose of prazosin due to postural hypotension.

Specific α blockers

Prazosin, terazosin and doxazosin

- Reversible highly selective α_1 blockers → relative absence of tachycardia as compared to phentolamine and phenoxybenzamine.
- Doxazosin preferred:
  - Longer acting[20].
  - Less 1st dose hypotension than prazosin & terazosin.

Tamsulosin & Alfuzosin

- Affinity for α_{1A} receptors on prostate & bladder neck muscle is higher than for vascular α_{1B} receptors → ↑efficacy in BPH with minimal change in BP → less postural hypotensive effect than other α blockers.

---

[20] $t_{1/2}$ 22 hours.

Centrally-Acting Sympatholytics

1. Methyl dopa

Mechanism of action:

- Prodrug → metabolized in the brain to α-methyl NE which stimulates central α_2 receptors in brain stem (NTS) → ↓ central sympathetic outflow.

Uses

- Antihypertensive especially in **pregnancy**.

Adverse effects: (limit its use)

1. Sympatholytic:
    - Sedation - dry mouth
    - Bradycardia.
    - Sexual dysfunction.
    - Diarrhea.
    - Peptic ulcer aggravation.
2. Hepatitis, hemolytic anemia, systemic lupus (immune based, less common).
3. Salt and water retention → tolerance & weight gain.
4. Depression (↓ DA, ↓ 5HT synthesis[21]).
5. Parkinsonism & hyperprolactinemia (↓ DA).

---

[21] Methyl dopa inhibits synthesis of DA, & 5HT by binding & inhibiting L-aromatic amino acid decarboxylase which is responsible for their synthesis .

2. Clonidine

Mechanism of action

1. Activates postsynaptic α_2 receptors in nucleus tractus solitarius and imidazoline receptors in rostral ventro-lateral medulla → ↓central sympathetic outflow → ↓ BP.
2. Acts on peripheral presynaptic α_2 receptors on adrenergic neurons → ↓ NE release.
3. Stimulates postsynaptic α_2 receptors → ↓ renin & aldosterone.

Uses

1. Diarrhea in diabetics with autonomic neuropathy.
2. Pre-anesthetic medication (sedative & analgesic).
3. Morphine withdrawal
4. Menopausal hot flushes.
5. Migraine prophylaxis
6. Hypertensive urgencies.

} ↓ Sympathetic discharge

7. Glucoma (apraclonidine & brimonidine)

Adverse effects

1. Sympatholytic
   - Sedation - dry mouth
   - Bradycardia.
   - Sexual dysfunction.
2. **Rebound hypertension**: treated by α & β blockers e.g. labetalol.
3. Salt and water retention → tolerance & weight gain.

CHOLINERGIC PHARMACOLOGY

Synthesis of Acetylcholine (ACh)

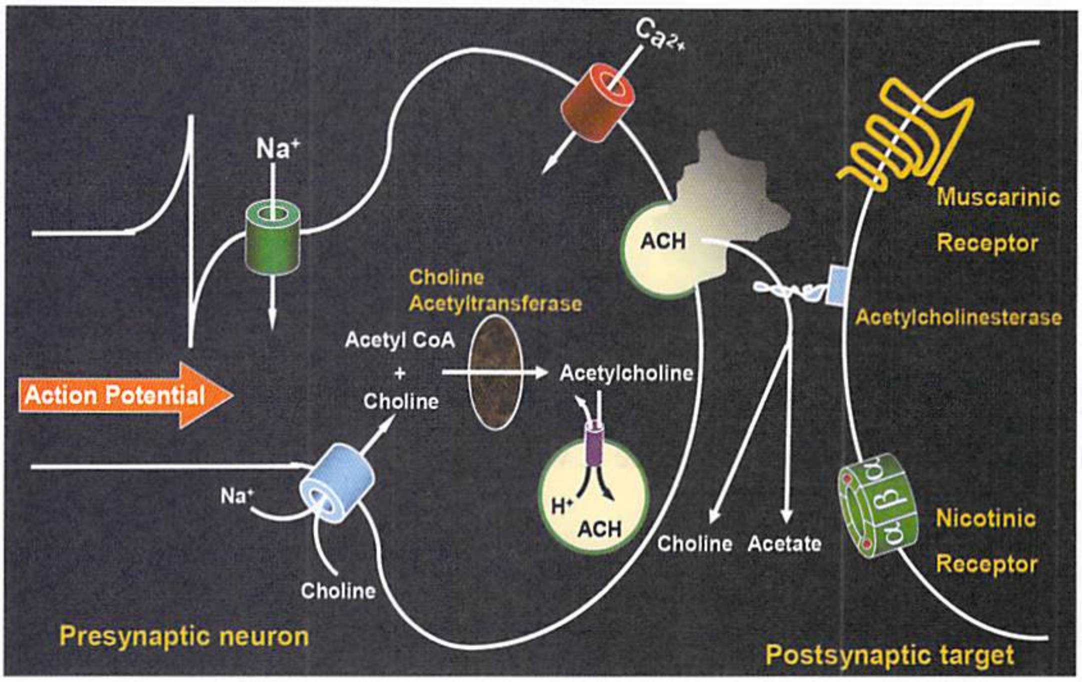
- Choline is transported by a membrane carrier from the extracellular fluid into the cholinergic neuron where it is acetylated in the cytoplasm by acetyl CoA forming ACh. The reaction is catalyzed by choline acetyl transferase.

Storage & Release of ACh

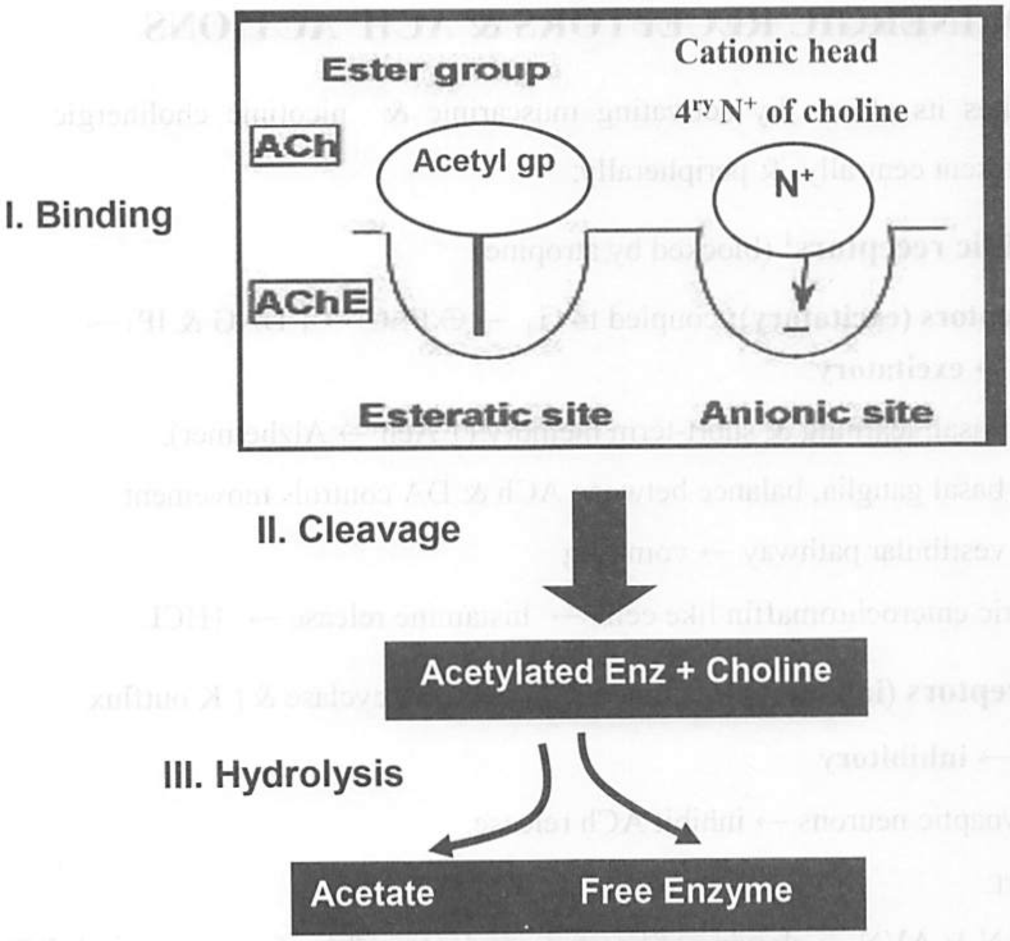
- ACh is stored in small membrane-bound vesicles, which are concentrated in the terminals of cholinergic neurons. Arrival of an action potential triggers Ca^{2+}influx, which stimulates release of ACh by partial exocytosis.
- Action of ACh is terminated by rapid hydrolysis by acetylcholine esterase.

Control of ACh release by presynaptic receptors

- M_2 inhibitory (dominant).
- N_n facilitatory (ensures continuous supply of Ach in motor nerves).
- α_2 inhibitory (explains relaxation of gut smooth muscles by α_2 agonists).


Ca2+
Na+
ACH
Muscarinic Receptor
Choline Acetyltransferase
Acetylcholinesterase
Acetyl CoA + Choline
Acetylcholine
Action Potential
Na+
H+
ACH
Choline
Acetate
Choline
α β α
Nicotinic Receptor
Presynaptic neuron
Postsynaptic target

Synthesis, Storage, Release & Fate of ACh


Ester group
Cationic head
4^{ry} N$^+$ of choline
ACh
Acetyl gp
N$^+$
I. Binding
AChE
Esteratic site
Anionic site
II. Cleavage
Acetylated Enz + Choline
III. Hydrolysis
Acetate
Free Enzyme

Degradation of Acetylcholine

- ACh is degraded by choline esterase enzyme through 3 steps:
  1. **Binding:** The acetyl (ester) group of ACh binds to the esteratic site of the enzyme by a covalent bond & the N$^+$ (cationic) head binds to the anionic site by a weaker ionic bond.
  2. **Cleavage**: choline is cleaved leaving the acetylated enzyme.
  3. **Hydrolysis:** hydration of acetylated enzyme releases acetate & the free enzyme.

Types of Choline Esterases

- **True (AChE)**: Present at terminals of cholinergic fibers & RBCs. Specific for ACh , essential for life with slow regeneration in 120 days.
- **Pseudo ChE**: Present in plasma. Nonspecific → hydrolyzes other esters as succinylcholine. Not essential for life, rapidly regenerated by the liver.

CHOLINERGIC RECEPTORS & ACH ACTIONS

- ACh mediates its effects by activating muscarinic & nicotinic cholinergic receptors present centrally & peripherally:

I. Muscarinic receptors[1] (blocked by atropine)

1. **M_1 receptors (excitatory):** coupled to G_q → ⊕ PLC → ↑ DAG & IP_3 →
   - CNS→ **excitatory**
     a. Arousal, learning & short-term memory (↓ Ach → Alzheimer).
     b. In basal ganglia, balance between ACh & DA controls movement.
     c. In vestibular pathway → vomiting
   - Gastric enterochromaffin like cells → histamine release → ↑HCL
2. **M_2 receptors (inhibitory):** coupled to G_i → ⊖ A cyclase &↑ K outflux
   - CNS→ **inhibitory**
   - Presynaptic neurons → inhibit ACh release.
   - Heart:
     a. SAN & AVN → slowing of heart -↓ conduction &↑ refractory period (RP).
     b. Atria →↓ contractility -↓ action potential duration - ↓ RP.
3. **M_3 receptors (excitatory):** coupled to G_q → ⊕ PLC → ↑ DAG & IP_3. →
   - Smooth muscles→ stimulate wall (bronchi, GIT, urinary) & relaxes sphincters.
   - Eye → miosis (⊕ constrictor pupillae) - accommodation (⊕ ciliary muscle).
   - Exocrine glands→ ↑ All secretions (except milk[2]).
   - Vascular endothelium → NO release → VD → ↓ BP.

II. Nicotinic receptors (excitatory): ligand-gated Na^+/K ion channels →

- **Neuronal (N_n):** in autonomic ganglia, presynaptic on motor nerves & in adrenal medulla → catecholamines release (blocked by etamon).
- **Muscle (N_m)** →skeletal muscle depolarization → contraction (blocked by curare).
- **CNS:** Renshaw cell (blocked by dihydro-beta-erythroidine) - ADH release.

---

[1] There are 5 subgroups of muscarinic receptors: M_1 - M_5

[2] Under control of prolactin & oxytocin.

- ACh lacks specificity, irregularly absorbed (4^{ry} drug) & rapidly hydrolyzed if given systemically→ only used after cataract surgery; instilled into eye → rapid & complete miosis (no choline esterase in aqueous humor).

CLASSIFICATION OF CHOLINOMIMETICS♦

I. Directly acting (on cholinergic receptors)

A. Choline Esters♦

- 4^{ry} drugs → low lipid solubility & poor CNS access.

- Not hydrolyzed by ChE → more stable than Ach:

1. **Methacholine** → marked muscarinic effects.
2. **Carbachol** → muscarinic & nicotinic effects.
3. **Bethanechol** → marked muscarinic effects on GIT & bladder→ prokinetic used in megacolon & urinary retention.

B. Natural Alkaloids

- **Pilocarpine**: 3^{ry} drug; selective M_3 agonist on:
  - **a. Eye**: miotic used for:
    - i. Counteracting mydriatics after fundus examination.
    - ii. Alternating with mydriatics in iridocyclitis to prevent synechia.
    - ii. Glaucoma (preferred →M_3 selective & long acting preparations, ocuserts are available)
  - **b. Exocrine glands**: ↑ secretion → used in dryness of eye & mouth.
  - **c. Scalp blood vessels**: VD→ used as hair tonic.

C. Cevemiline

- Selective M_3 agonist → used in dryness of eye & mouth.

II. Indirect Choline Esterase Inhibitors (ChEIs)

♦ Methacholine & bethanechol have weak nicotinic actions due to extra methyl group. Carbachol is used in glaucoma & post operative paralytic ileus & urine retention (rarely).

CHOLINE ESTERASE INHIBITORS

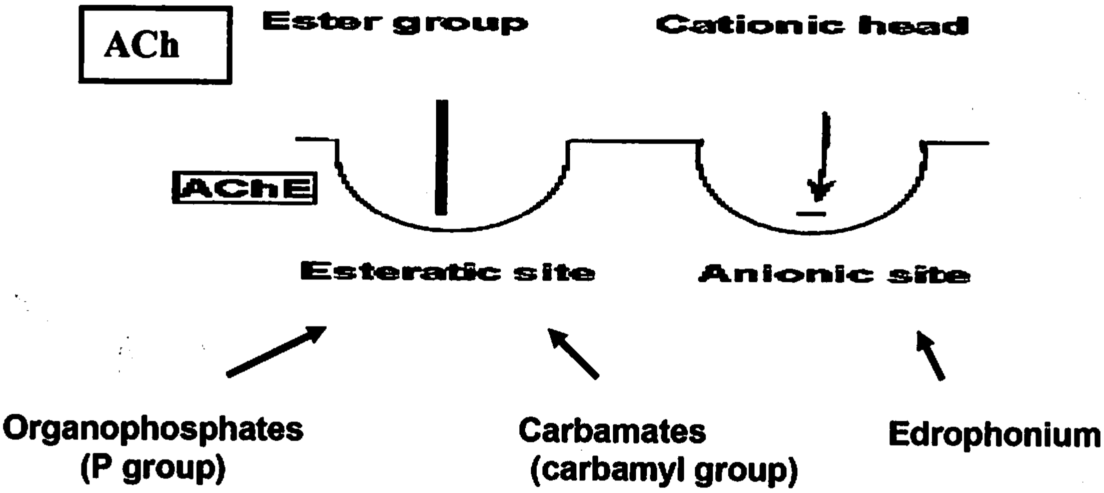
ChEIs

Mechanism of Action

- ChEIs act indirectly by inhibiting choline esterase → accumulation of ACh.
- Neostigmine has also direct effect on Nm receptors at NMJ.

Individual ChEIs

1. **Edrophonium** (weak, short-acting, 2-10 min - reversible)
    - Binds electrostatically to the anionic site of enzyme with rapid hydrolysis.
2. **Carbamate Esters** (medium-duration, 3-4 hours- reversible)
    - The carbamoyl group binds covalently to esteratic site of enzyme (active site) → carbomoylated enzyme (covalent bond is more resistant to hydrolysis).
3. **Organophosphates** (very long duration - irreversible)
    - The phosphate group binds irreversibly to the esteratic site of the enzyme.
    - The covalent phosphorous enzyme bond is extremely stable and hydrolyzes in water at a very slow rate (hundreds of hours).
    - Ageing occurs in the phosphorylated enzyme bond within 2 minutes - 12 hours, after which recovery of enzyme cannot occur (strengthening of covalent bond). Thus, choline esterase regenerators in organophosphate poisoning should be given early before ageing occurs.


ACh
Ester group
Cationic head
AChE
Esteratic site
Anionic site
Organophosphates
(P group)
Carbamates
(carbamyl group)
Edrophonium

CLASSIFICATION & USES OF ChEIs[♠]

Reversible

Simple Alcohols

Edrophonium (4^{ry} compound)

- Short-acting → used in diagnosis of myasthenia gravis.

Carbamates

1. **Neostigmine** (synthetic; stable)
   - 4^{ry} → poorly absorbed - cannot cross BBB or conjunctiva.
   - **Muscarinic effects**: on bladder & GIT→↑ peristalsis in post operative paralytic ileus & urine retention.
   - **Nicotinic effects**: ↑ skeletal muscle power, used in:
     - i. Myasthenia (preceded by atropine to ⊖ muscarinic side effects).
     - ii. Antidote to neuromuscular blockers (preceded by atropine).
2. **Physostigmine** (natural; unstable)
   - 3^{ry} amine→ well absorbed, crosses BBB & conjunctiva.
   - **Muscarinic effects**:
     - a. Miotic: i. counteracts mydriatics e.g. after fundus exam.
       ii. ↓ IOP in glaucoma.
     - b. Atropine toxicity (central & peripheral atropine antagonist).

Irreversible

Organo-phosphates

- **Malathion** (Insecticides).
- **Sarin** (Nerve gas)
- **Echothiophate**:
  - i. Antagonizes atropine[♠] after fundus exam.
  - ii. Glaucoma

Pyrantel pamoate

- Paralysis of round worms

- **Donepezil, rivastigmine:** used in Alzheimer dementia.
- **Pyridostigmine:** neostigmine analogue preferred in myasthenia [1] (↑duration, fewer visceral side effects; ↑ selectivity on skeletal muscles compared to neostigmine).

[♠] Ecothiophate is the only CHEI that can antagonize atropine after fundus examination.

[1] Autoimmune disease of skeletal muscles → antibodies that ↓ number of nicotinic receptors on motor end-plate → weakness of extraocular, bulbar, neck, followed by other muscles.

Uses

1. **Alzheimer**
   - Rivastigmine
2. **Atropine toxicity**
   - Physostigmine
3. **Miotics:**
   - a. Glaucoma
   - b. To counteract mydriatics
   - Pilocarpine.
   - Physostigmine
   - Ecothiophate
4. **Dry eye &mouth**
   - Pilocarpine
   - Cevemiline
5. **Hair tonic**
   - Pilocarpine
6. **Megacolon**
   Bethanechol
7. **Post operative Paralytic ileus Urine retention**
   - Neostigmine.
   - Bethanechol
8. **Myasthenia & Antidote for NM blockers**
   - Neostigmine

Actions of Cholinomimetics

1. **CNS (M$_1$)** Ach is excitatory →
   - Arousal & short term memory.
2. **Eye (M$_3$)**
   - Miosis (⊕ constrictor pupillae).
   - Accommodation (⊕ ciliary muscle)
   - Above effects → ↑ outflow of aquous humor →↓IOP.
3. **Exocrine Glands (M$_3$)**
   - ↑ Salivary, sweat, bronchial, lacrimal & HCl secretion.
4. **Heart (M$_2$)**
   - Bradycardia – AV block
   - ↓ Atrial contractility
   - ↓ Atrial refractory period (↑conduction)
5. **Vascular endothelium (M3)**
   - Release of EDRF → VD.
6. **Smooth muscles (M3)**
   - Bronchospasm.
   - ⊕ bladder wall & GIT motility & ⊖ sphincters → micturition, defecation.
7. **Skeletal muscle (Nicotinic)**
   - Depolarization → contraction
   - High concentration → persistent depolarization block→ paralysis.

Adverse Effects Contraindication (CI)

1. Irritability Convulsions (with agents that cross BBB)
2. Miosis
3. Lacrimation -salivation, ↑HCl → CI peptic ulcer
4. Bradycardia Cardiac arrest (→ never given IV) CI Infarction
   → Precipitate atrial fibrillation in thyrotoxic pt.(avoid)
5. Bronchospasm
   CI Asthma
6. ↑ Urination- diarrhea colic- N & V
   CI: urinary or intestinal obstruction (→ rupture)
7. Lid twitches, browache, frontal headache (with eye drops)
8. Fasciculations
9. paralysis

Toxicity of Organophosphorus Compounds

- Organophosphorus compounds are highly lipid-soluble & are well absorbed from all sites & cross BBB (echothiophate has 4^{ry} N^+ → ↓systemic toxicity).
- Poisoning occurs due to suicide or exposure to drugs during spraying insecticides (Parathion, Malathion) or nerve gases (sarin) during war.

Acute toxicity

- **Excessive muscarinic effects (see table)**[5]
- **Nicotinic effects:** fasciculation & flaccid paralysis.
- **CNS effects**: stimulation (convulsions) → depression (coma & respiratory depression).

Death is due to respiratory failure:

- Respiratory center depression.
- Paralysis of respiratory muscles due to persistent depolarization block.
- Excessive bronchial secretions with **acute pulmonary oedema**.

Chronic Toxicity: Chlorpyrifos & Malathion[6]→ delayed neuropathy.

Treatment of Organophosphorus Poisoning

1. **Maintain vital signs**:
   Aspirate bronchial secretions, endotracheal intubation & artificial respiration.
2. **Decontamination** (to prevent further absorption):
   Remove contaminated clothes - wash skin (Na hypochlorite) - gastric lavage.
3. **Atropine** (large doses) for CNS & muscarinic effects:
   2 -5 mg/ 5 min → full atropinization (until bronchial secretions & wheezes stop).
4. **Choline esterase reactivators (oximes): PAM** (pralidoxime)
   Regenerates choline esterase (IV infusion as soon as possible before its ageing).
5. **Diazepam**: for convulsions.

---

[5] Heart rate may be↓ or ↑ (due to sympathetic⊕). The 1st symptom on exposure to nerve vapor may be rhinorrhea & to nerve liquid is sweating.

[6] In houshold insectisides sprays (e.g. raid).

ANTIMUSCARINIC AGENTS

Atropine & Atropine Substitutes

Atropine

- It is a tertiary ammonium ester of tropic acid → well absorbed from the gut if given orally or from conjunctiva after occular instillation & can cross BBB.

Mechanism of Action

- Atropine causes reversible competitive blockade of the actions of ACh at muscarinic receptors (nonselective for muscarinic receptors).

Pharmacological Actions

1. CNS

- Stimulates cardioinhibitory center (vagal nucleus)→initial bradycardia
- Respiratory center stimulation (blocks M_2 receptors) .
- Antiemetic (blocks M_1 receptors in vestibular pathway).
- Antiparkinsonian (blocks M_1 receptors in basal ganglia).

2. Eye (effects persist for > 72 hrs)

- **Mydriasis** [7](paralysis of constrictor pupillae).
- **Cycloplegia** (ciliary muscle paralysis & loss of accommodation for near vision).

↓ Aquous out flow →↑ IOP → acute glaucoma in narrow anterior chamber

3. Secretions

- ↓ Salivation (→ dry mouth), ↓ lacrimation (→ dry sandy eyes).
- ↓ Sweating (→↑ body temperature) & ↓ bronchial secretions.
- Gastric secretion is least affected while milk secretion is unaffected.

4. Smooth Muscle

- GIT: relaxes wall & contracts sphincters → constipating & antispasmodic.
- Bladder neck: contraction of urinary bladder sphincter→ urine retention.
- Bronchodilation.

---

[7] Passive, due to unopposed sympathetic activity on dilator pupillae

5. CVS

- **Tachycardia** (mainly) & ↑AVN conduction (blocks M_2 receptors).
- **Initial bradycardia**: initial agonist activity → central vagal stimulation
  presynaptic M_2 block → ↑ ACh release.
- **Vasodilation** (due to histamine release).

Clinical Uses of Atropine & atropine Substitutes

Atropine

Therapeutic Uses

1. Preanesthetic medication →inhibits secretions - dilates bronchi - anti-emetic - inhibits reflex bradycardia - stimulates respiration.
2. Hyperactive carotid sinus - heart block - bradycardia (in infarction or digitalis toxicity).
3. Organophosphate poisoning - mushroom poisoning (*Amanita muscaria*).
4. Cycloplegic in children (atropine is preferred to atropine substitutes in children as their ciliary muscle is strong & atropine substitutes are weaker cycloplegics than atropine).
5. Travelers diarrhea (plus diphenoxylate, an opioid antidiarheal) to enhance its constipating effect & to decrease its abuse.

Atropine Substitutes

I. Scopolamine (Hyoscine)

Uses

- Mydriatic (briefer than atropine).
- Vomiting of motion sickness & Minieres disease (preferred as it is more effective than atropine).
- Preanesthesia in thyrotoxic & cardiac patients (pure antagonist; no initial bradycardia).

- Natural atropine substitute.
- More CNS depressant than atropine → drowsiness & amnesia.
- May induce CNS excitement & hallucination when used as preanesthetic in females → vivid dreams.

II. Synthetic atropine substitutes (more selective → fewer side effects)

1. **Mydriatic cycloplegics** (cyclopentolate -tropicamide – homatropine) for:
   - Iridocyclitis; alternating with miotics to prevent synechia (homatropine).
   - Measuring refractive errors & for fundus examination[8].

   N.B. : they are shorter acting than atropine → action is easier to reverse → preferred to atropine (except in children).

2. **Antisecretory antispasmodics:**

   4ry drugs (→ less absorption → less CVS & CNS side effects)
   - **Glycopyrrolate**: anti-secretory in preanaesthetic medication & before neostigmine to ↓side effects during reversal of action of NMBs.
   - **Hyoscine butylbromide**: antispasmodic in renal, biliary & intestinal colic & in irritable bowel syndrome.

   3ry drugs: **Dicyclomine**; selective M_1 blocker → antispasmodic

3. **Urinary atropine substitutes:**
   - **Oxybutynin**: used in nocturnal enuresis & in urge incontinence.

4. **Anti-parkinsonian** (benztropine - benzhexol): Used in
   - Drug induced Parkinsonism: preferred to dopaminergic drugs.
   - Adjuvants in Parkinsonism presenting with tremors & to control sialorrhea.

5. **Bronchial atropine substitutes**

   Ipratropium (non selective M_2 / M_3 blocker)
   - Inhaled bronchodilator (M_3 blocker) → no systemic atropine side effects.
   - Used in asthma & COPD: delayed onset compared to beta 2 agonists.
   - Tolerance develops due to block of vagal presynaptic M_2 receptor →↑ ACh.

   Tiotropium (selective M_3 blocker)
   - Longer acting than ipratropium → used once/d; for maintenace in COPD.
   - Does not block M_2 receptors → no tolerance.

---

[8] Mydriatic effect is required for fundus examination; miotics are given later to antagonize their effect. Cycloplegia is required for measurement of refractive errors.

Adverse effects of atropine → poisoning (Contraindications; CI)

1.Confusion, restlessness → hallucinations, delirium & mania→ ***Mad as a hen.***

2. Dry mouth and skin →***Dry as a bone.***

3. Hyperthermia (complete skin dryness) →***Hot as a hare.***

4. Vasodilation & flushing →***Red as a beet.***

5. Tachycardia.

6. Blurred vision - photophobia→ ***Blind as a bat.***

7. Acute glaucoma in patients with narrow anterior chamber **(CI: glaucoma).**

8. Urine retention in old patients with enlarged prostate **(CI: enlarged prostate).**

9. Constipation.

Treatment of atropine poisoning

- Gastric lavage.
- Physostigmine (antagonizes central & peripheral effects).
- Diazepam: to control CNS excitement.
- Cooling blankets: to treat hyperthermia in children (not aspirin).

Drugs with Atropine-Like Action

- Antiarrhythmics: quinidine - procainamide – disopyramide.
- Antihistamines (1st generation).
- Tricyclic antidepressants – antipsychotics– pethidine.
- Atropine substitutes.

SKELETAL MUSCLE RELAXANTS

- Drugs affecting skeletal muscle tone could be classified into 2 major divisions:
  1. **Neuromuscular blockers** (mainly used as adjuncts to anesthetics).
  2. **Spasmolytic drugs** (mainly used in spastic disorders of skeletal muscles).

NEUROMUSCULAR BLOCKERS (NMBs)

They are classified into 2 groups:

1. **Nondepolarizing** NMBs → prototype: *d*-tubocurarine.
2. **Depolarizing** NMBs → prototype: succinylcholine.

Therapeutic Uses of NMBs

1. Adjuncts to general anesthesia: induce muscle relaxation → facilitating incision, decreasing cough & laryngospasm & allowing reduction of the dose of the general anesthetic (nondepolarizing NMBs).
2. To assist mechanical ventilation (nondepolarizing NMBs→ paralyze respiratory muscles so as not to interfere with mechanical ventilation).
3. Facilitation of endotracheal intubation

   Succinylcholine is 1st choice→ rapid action[9] →↓ risk of vomiting & aspiration of gastric contents (rocuronium is an alternative)
4. Electroconvulsive therapy:

   Control convulsions → ↓ pain & injury (succinylcholine is 1st choice[10]).

- Succinylcholine has a rapid onset of action (1 min) & is short acting (5-10 min) due to rapid hydrolysis by pseudo ChE in plasma & liver, thus it is reserved for short procedures; given by IV injection or infusion.

---

[9] Rapid action of the drug allows rapid intubation & removal of oxygen mask (oxygen mask →↑ risk of passage of oxygen to GIT with increased risk of vomiting & aspiration pneumonia).

[10] Short acting competitive neuromuscular blockers are also used.

Nondepolarizing (Competitive) Neuromuscular Blockers

Mechanism of Action

- **Small dose**: competitive blockade of Nm receptors at motor end plate.
- **Large dose**: Block presynaptic Nn receptors →↓ ACh release.
  Block ion channels of Nm receptors.

D-Tubocurarine (prototype)

- Produces flaccid paralysis lasting more than 35 min (long-acting).
- Small muscles of face, eye and neck are affected first and diaphragm last.
- Recovery occurs in the reverse order (diaphragm first).
- **Effects are antagonized by:**
  - Neostigmine: given at the end of operation to reverse the action of the NMB (preceded by atropine to prevent bradycardia & cardiac arrest).
- **Effects are potentiated by:**
  - Anesthetics, e.g. halothane, ether (stabilize motor end-plate).
  - Antibiotics, e.g. aminoglycosides (inhibit ACh release).

Adverse Effects and Precautions

1. Histamine release:
   - Bronchoconstriction **(CI: bronchial asthma).**
   - Allergy **(CI: allergic patients).**
   - Hypotension
2. Ganglion blockade → hypotension.
3. **CI in renal disease** (clearance depends on renal excretion).

Toxicity of Competitive Neuromuscular Blockers

- Respiratory muscle paralysis and hypoxia; treated by:

1. Artificial respiration.
2. Neostigmine, preceded by atropine to prevent bradycardia & cardiac arrest.

Newer NMBs:

- More potent than curare (except rocuronium) with no ganglion blockade & less (atracurium) or no histamine (HI) release.

1. **Pancuronium (long acting)**
   - Avoid in renal & CV diseases (excreted renally; vagolytic effect→↑HR).
2. **Atracurium** (intermediate duration; used for short procedures)
   - May be given in renal or liver disease as it undergoes spontaneous breakdown (Hoffman's reaction) in addition to its hepatic metabolism.
   - **Cisatracurium**: less histamine release than atracurium →fewer side effects.
3. **Vecuronium** (intermediate duration; used for short procedures)
   - May be given in renal but not in liver diseases (clearance is mainly hepatic).
   - Offers cardiovascular stability preferred in CV diseases.
4. **Rocuronium** (intermediate duration; 20-35 min)
   - Similar to vecuronium.
   - Rapid onset of action → alternative to succinylcholine for endotracheal intubation.
5. **Mivacurium** (short acting; 10- 20 min)
   - Hydrolyzed by pseudo ChE (↓enzyme in renal disease→ prolongs effect).
   - Slower onset than succinylcholine; if dose is increased to speed onset → ↑ histamine release.
6. **Gantacurium** (rapid onset, very short duration of action)
   - Profile similar to succinylcholine→ used for endotracheal intubation & mechanical ventilation.
   - Action is terminated by cysteine amino acid adduction followed by slow non enzymatic hydrolysis. Thus, its action can be reversed with cysteine.
   - Releases histamine at doses 3 times the ED-50.

Reversal of effects of neuromuscular blockers post operatively

1. **Neostigmine**: preceded by atropine or glycopyrolate.
2. **Sugammadex:**
    - Encapsulates rocuronium & vecuronium in its lipophyllic core, allowing a conc. gradient between plasma & NMJ, so NMBs diffuse away from NMJ. The complex is then excreted in urine.
    - **Advantages over neostigmine**: faster reversal with fewer side effects (not preceded by anti-muscarinics, avoiding their troublesome side effects.
3. **Cysteine:** reverses the action of gantacurium

Depolarizing Neuromuscular Blockers

Succinylcholine

Mechanism of Action

Initial fasciculations (transient twitches):

- Succinylcholine binds to nicotinic receptors at NMJ→ initial depolarization (fasciculation).

Phase I: Depolarization block

- Succinylcholine induces persistent depolarization of motor end plate since it is slowly hydrolyzed by pseudo ChE (compared to ACh).

Phase II: Desensitization block (antagonized by neostigmine)

- On prolonged use, the membrane repolarizes but receptors are desensitized to ACh (due to unknown cause).

N.B.: muscles are paralyzed in the same order as with competitive NMBs.

Adverse Effects and Contraindications (CI)

1. **Succinylcholine apnea**
   - Genetic abnormality of pseudo ChE (or ↓ pseudo ChE due to liver disease or malnutrition) → failure of succinylcholine breakdown → prolonged respiratory muscle paralysis → apnea.

   Management: Support ventilation

   Phase I block → blood transfusion (to supply enzyme).

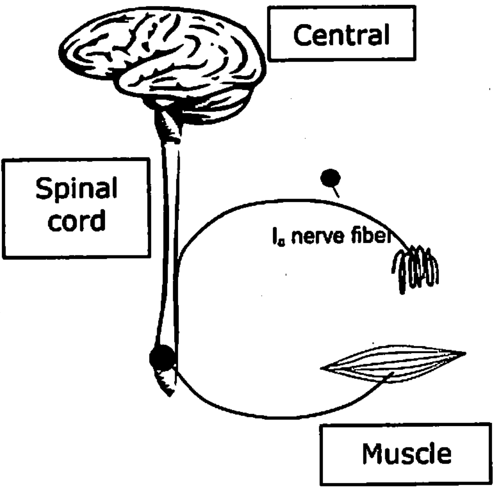
   Phase II block → neostigmine preceded by atropine.

2. **Fasciculations** →
   a. Postoperative muscle pain (muscle damage due to unsynchronized contractions→ **CI:** extensive muscle trauma.
   b. ↑ IOP → **CI:** narrow-angle glaucoma and penetrating eye injuries.
   c. ↑ Intra-gastric pressure → vomiting with aspiration of gastric contents.
   d. Hyperkalemia → cardiac arrest → **CI:** burns & trauma (↑ K^+ outflux).
3. **Bradycardia.**
4. **Malignant hyperthermia** (genetic defect)
   - Skeletal muscles fail to sequester Ca^{2+} in sarcoplasmic reticulum following administration of succinylcholine & halothane →
     - ↑ Muscle contractions (treated by spasmolytics as dantrolene).
     - Hyperthermia (treated by cooling blankets).
     - ↑ Lactic acid (correct acidosis, water & electrolyte disturbance).

CI: in patients with a family history of malignant hyperthermia & succinylcholine apnea

SPASMOLYTICS

- Spasmolytics are drugs that reduce muscle tone with minimal effect on active contractions [11].



Causes of spasticity (uses of spasmolytics)

1. **Central causes**[12]
    - Cerebral palsy - stroke (hemiplegia).
    - Multiple sclerosis - spinal cord injury
2. **Local causes**: Muscle trauma – inflammation
3. **Low back pain.**
4. **Drug induced**: malignant hyperthermia.

Classification of spasmolytic drugs

A- Centrally Acting

i. Diazepam: GABA - A agonist used in most causes of spasticity.

Side effects: sedation & tolerance.

i. Baclofen: GABA- B agonist at spinal synapses.

Uses: multiple sclerosis & spinal cord injuries.

Side effects: sedation less than diazepam.

iii. Tizanidine : α_2 agonist→ ↑ presynaptic inhibition of motor neurones in the cord → used in multiple sclerosis or after stroke.

iv. Orphenadrine: acts in the brainstem→ used for acute muscle spasm due to trauma or strain (→ anticholinergic side effects).

B- Peripherally acting

i. Dantrolene

- Inhibits Ca^{2+} release from the sarcoplasmic reticulum in skeletal muscle.
- Marked muscle weakness →limits its use to malignant hyperthermia.

ii. Botulinum toxin:

- Inhibits ACh release→ used locally in cosmetic therapy for wrinkles.

---

[11] NMBs → loss of both muscle tone and active contraction.

[12] Upper motor neuron lesion, with damage to descending pathways in the spinal cord →hyperexcitability of the alpha motoneurons in the cord.

AUTACOIDS

- Autacoids are groups of chemically diverse substances produced by various tissues in the body and act as local hormones. The most important autacoids are:
  - **Biologically active amines** e.g. Histamine and Serotonin.
  - **Vasoactive polypeptides** e.g. Angiotensin and Kinins.
  - **Eicosanoids** e.g. Prostaglandins and Leukotrienes.

HISTAMINE

(HI)

Synthesis:

- Histamine is synthesized by decraboxylation of the amino acid L-histidine with L-aromatic amino acid decarboxylase enzyme.

$$\text{L- Histidine} \xrightarrow{\text{Decarboxylase}} \text{Histamine}$$

Storage:

- Histamine is stored in storage granules inside mast cells (in most tissues e.g. lung, skin & GIT).

Release:

- **Histamine liberation:** HI liberators are basic drugs (e.g. morphine, atropine, curare, and hydralazine) that replace HI in storage granules without degranulation.

- **Immunogenic release:** interaction of antigenic drugs (e.g. **penicillin**) with IgE on surface of sensitized mast cells results in increase in intracellular calcium & release of the whole histamine- containing granules (exocytosis).

Pathogenic role of histamine

1. **Allergy:**

   Histamine stimulates H_1-receptors →immediate hypersensitivity reactions:

   a. **Local allergic response:** localized H_1 receptors stimulation on blood vessels & nerve endings →
      i. Arteriodilatation → redness.
      ii. Venodilatation →↑ capillary permeability & edema.
      iii. Sensory nerve stimulation → pain & itching.

   b. **Anaphylactic shock:** generalized H_1 receptors stimulation → marked arterial dilatation & hypotension.

   c. **Bronchial asthma:** H_1 receptors stimulation on bronchial smooth muscles → bronchospasm.

2. **Vomiting of vestibular origin** (e.g. motion sickness) is H_1-receptor mediated.

3. **Peptic ulcer:** H_2 receptors mediate more than 70% of HCl secretion.

Drugs that antagonize the action of histamine

1. **H_1 receptor blockers** (anti-histamines): for allergic reactions; see below.

2. **H_2 receptor blockers** (e.g. famotidine): for acid-related disorders; see GIT.

3. **Mast cell stabilizers & β_2 agonists**: inhibit immunogenic HI release; see respiratory pharmacology.

4. **Epinephrine**: physiological antagonism.

H_1-receptors Blockers (Antihistamines)

First Generation Antihistamines

Chlorpheniramine - promethazine - dimenhydrinate - doxylamine

Mechanism	Actions	Therapeutic uses	Adverse effects
1. H_1-receptor Inverse Agonist	**a. Anti-allergic** Block H_1 mediated allergy.	**Allergic reactions**[1]: • Rhinitis. • Urticaria. • Anaphylactic shock	
	b. CNS Depression 1. Sedation 2. Antitussive	• As OTC hypnotic. • Dry cough.	• Drowsiness; • Agitation (in children).
2. Muscarinic Receptor Blockade	**a.** Antiemetic	• Motion sickness. (Dimenhydrinate) • Pregnancy Vomiting (Doxylamine)	• **Atropine-like side effects**: Dry mouth Confusion Urine retention Constipation, Imbalance.
	b. Antiparkinsonian	Parkinsonism	
3. α- Blockade			• Postural hypotension

---

[1] Antihistamines are ineffective in asthma →can not antagonize leukotrienes or excessive HI released.

New generations Antihistamines

Azelastine[2], fexofenadine, cetirizine, loratadine, desloratadine

- Used in allergic conditions.
- Less lipophilic → less crossing of blood brain barrier → **less sedation**.
- Delayed elimination →**prolonged action** that permits single daily dosing.
- Still have varying degrees of autonomic effects.
- High doses can cross BBB → sedation.

---

[2] It may be preferred by some patients with allergic rhinitis as it is available as a nasal spray.

SEROTONIN

Synthesis:

$$\text{Tryptophan} \xrightarrow{\text{Tryptophan hydroxylase}} \text{5 – OH - tryptophan} \xrightarrow{\text{Decarboxylase}} \text{serotonin (5HT)}$$

Storage:

- In GIT enterochromaffin cells, CNS neurons, and in platelets.

Release:

- Released from blood platelets following platelet activation e.g. by thrombin.
- Released from CNS neurons on nerve stimulation.

Metabolism:

- By oxidation with MAO into 5-hydroxyindole acetic acid; "5HIAA".
- **Urinary 5-HIAA** is used in diagnosis[3] of carcinoid syndrome (excess 5HT).

Reuptake:

- Serotonin is re-uptaken by nerve endings in the CNS by the monoamine pump.

Serotonin receptors & pathogenic role of serotonin

1. **Anxiety: presynaptic** $5HT_{1A}$ receptors stimulation in the limibic system → reduces 5HT release→ reduces anxiety.
2. **Migraine:** $5\text{-}HT_{1B/1D}$ receptors stimulation on cranial blood vessels and trigeminal nerve endings terminates acute migraine attack.
3. **GIT motility disorders:** prokinetics stimulate $5\text{-}HT_4$ receptors.
4. **Carcinoid syndrome:** 5HT ⊕ smooth muscles → bronchospasm & diarrhea.
5. **Psychosis:** atypical antipsychotics block $5\text{-}HT_2$ receptors.
6. **Depression:** antidepressants →↑ central 5-HT e.g. TCA, SSRI, NSRI, MAOIs.
7. **Vomiting:** $5\text{-}HT_3$ receptors mediate cytotoxic drug-induced emesis.

---

[3] Also used in diagnosis of heparin-induce thrombocytopenia: normal platelets radiolabeled with 14 C-serotonin are challenged with patient's serum & heparin. Release of 14C-serotonin signifies a positive test.

Drugs acting through serotoninergic mechanisms

1. **Drugs inhibiting 5-HT reuptake →↑ central 5-HT; used mainly in depression**
   - Selective serotonin reuptake inhibitors (SSRI) or non selective inhibitors e.g. norepinephrine-serotonin reuptake inhibitors (NSRI) & tricyclic anti-depressants (TCA).

2. **Serotonin receptor agonists**
   - **a.** 5-HT_{1A} agonists: Buspirone → selective anxiolytics.
   - **b.** 5-$HT_{1B/1D}$ agonists: Triptans & Ergots → anti-migraine drugs.
   - **c.** 5-HT_4 agonists: Tegaserode → prokinetic in irritable bowel syndrome.

3. **Serotonin receptors blockers**

   a. Selective 5HT_2 receptor blockers [4]

   - **Cyproheptadine & pizotifen**: block 5HT_2 & H_1 receptors. **Used in**:
     i. Carcinoid syndrome & serotonin syndrome (excess 5HT).
     ii. OTC appetizers.
     iii. Migraine prophylaxis.
   - **Atypical antipsychotics** (e.g. resperidone) (also block D_2 receptors).

   b. Selective 5HT_3 receptor blockers

   - **Ondanosetron** (antiemetic).

Toxicity of serotonin

1. **Serotonin syndrome** (acute serotonin toxicity)
   - Tremors, convulsions & hyperthermia (life threatening): due to ↑ 5-HT activity at postsynaptic 5-HT_{1A} & 5-HT_{2A} receptors in the CNS on administration of two serotonergic agents simultaneously, or a toxic dose of a single drug (SSRI).

---

[4] Ketanserin is a selective 5HT_{2A} blocker rarely used in hypertension (as it is an α-blocker) & pre-eclampsia. Some antidepressants (e.g.mirtazapine, trazodone) block 5HT_2 receptors.

2. **Valvular heart disease** (chronic serotonin toxicity)
   - 5-HT stimulates fibrogenesis → thickening of cardiac valves.
   - Occurs on long term treatment with serotonergic drugs (e.g. ergots).

MIGRAINE AND ANTIMIGRAINE DRUGS

- An attack of migraine starts by a **prodroma** (irritability, fatigue, muscle aches), followed by an **aura** (visual disturbances; scotoma) and in 30 minutes by throbbing headache; starting unilaterally with nausea, vomiting & photophobia.
- Migraine is triggered by stress, hormonal changes (menstruation), disturbed sleep pattern, weather changes & alcohol.

Pathophysiology of migraine (not fully understood)

- Migraine may be due to release of pro-inflammatory vasodilatory neuropeptides (e.g., CGRP) from nerve endings of trigeminal nerve into the perivascular space → dilation of dural vessels → stretch of pain nerve endings.

Drugs used to terminate acute migraine attack

I. Mild analgesics: NSAIDs & acetaminophen (for mild infrequent attacks).

II. Triptans: "specific" antimigraine therapy: therapy for outpatients with moderate to severe migraine is begun with a triptan.

Mechanism of action (selective $5HT_{1B/1D}$ agonists)

1. Activate $5HT_{1B/1D}$ receptors on presynaptic trigeminal nerve endings to inhibit release of vasodilatory neuropeptides.
2. Vasoconstriction of dural vessels → prevent stretching of pain nerve endings.

Preparations of triptans

Sumatriptan: prototype [5] (oral, SC, nasal spray)

Adverse effects:

1. Injection site reaction (with SC) or unpleasant taste (with intranasal).
2. Chest pressure (resolves spontaneously in 30 minutes).
3. Paresthesias, warmth, drowsiness, dizziness, weakness, malaise.

Contraindications & Precautions

1. Uncontrolled hypertension, ischemic stroke & IHD → 1st dose given cautiously in diabetics, hypertensives, men over 40 & in postmenopausals.
2. Pregnancy.
3. With serotoninergic drugs: SSRIs or within 24 hrs of ergots → 5HT syndrome).

III. Ergots: $5HT_{1B/1D}$ agonists similar to triptans

1. Ergotamine tartrate (sublingual, oral, rectal); of choice in prolonged or frequent headaches.
2. Dihydroergotamine (IV, IM, SC & intranasal).

Adverse effects & contraindications of ergots:

- GIT: Nausea, vomiting, diarrhea.
- Chest pressure.
- Vasospasm→ gangrene (CI peripheral vascular disease).
- CI. Pregnancy.
- Should not be used for long term (→ valvular heart disease).

IV. Antiemetics

- Parenteral metoclopramide (monotherapy in emergency; if ineffective add IV dihydroergotamine).
- Oral metoclopramide → added to other antimigraine drugs (ergotamine) to increase their absorption by its prokinetic effect.

V. Benzodiazepines & opioids

- Used in resistant cases (may lead to habituation & rebound headache).

---

[5] Zolmitriptan (nasal & oral), naratriptan, rizatriptan, almotriptan, eletriptan, frovatriptan (oral).

Drugs for migraine prophylaxis [6]

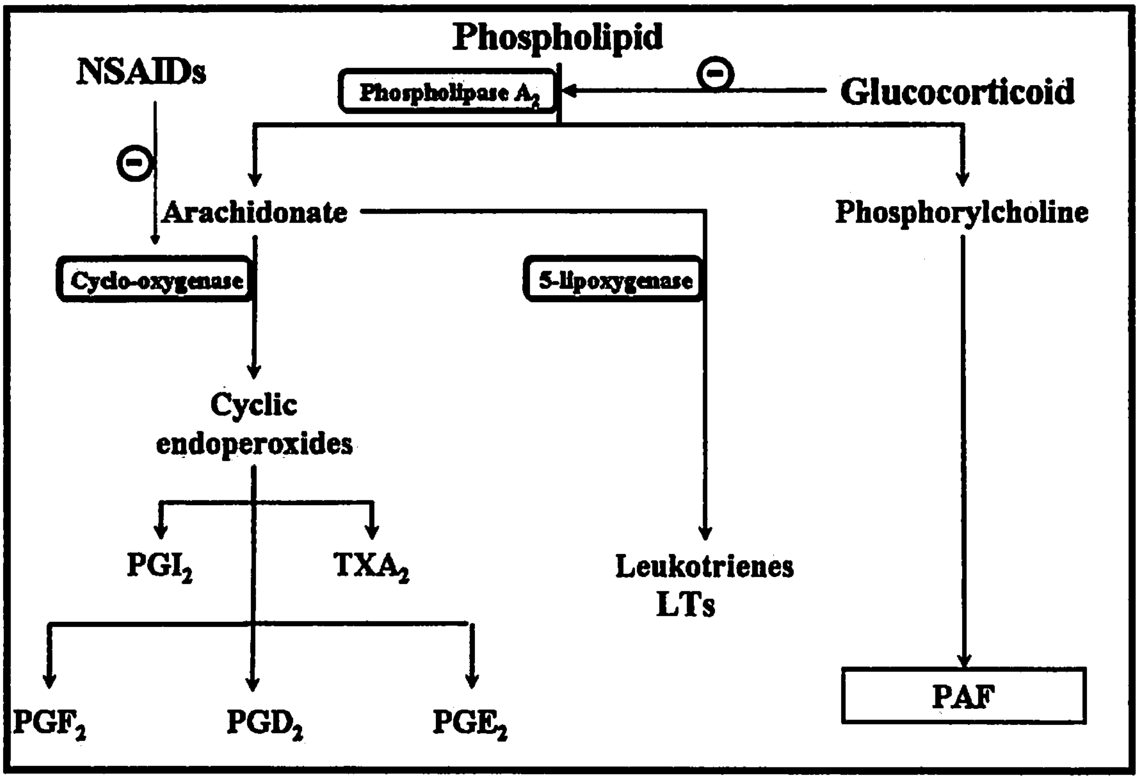
- Anti-migraine therapy should not exceed 10 days /month to avoid medication overuse headache "MOH". Prophylactic drugs should then be administered:

  1. **Beta blockers**: propranolol and timolol: are of choice
  2. **Antidepressants**: amitriptyline
  3. **Anticonvulsants:** valproate & topiramate. (↓ Excess firing of trigeminal nerve).
  4. **Calcium channel blockers:** nifedipine, verapamil (→ tolerance).

---

[6] Other agents which may be used (but not FDA-approved) include 5HT antagonists e.g. pizotifen, mirtazapine, ACE inhibitors, angiotensin receptor blockers & botulinum toxin.

Prostaglandins (PGS) and Thromboxanes (TXS)


Phospholipid
NSAIDs
Phospholipase A₂
⊖
Glucocorticoid
⊖
Arachidonate
Phosphorylcholine
Cyclo-oxygenase
5-lipoxygenase
Cyclic endoperoxides
PGI₂
TXA₂
Leukotrienes LTs
PGF₂
PGD₂
PGE₂
PAF

Biosynthesis of Eicosanoids (PGs, TXs & LTs) & Platelet Activating Factor

- PGs & TXs are endogenous 20-C (eicosanoid) fatty acid derivatives with profound physiological effects. They are involved in:
  - Inflammation - thermoregulation.
  - Regulation of: platelet function - vascular tone - bronchial tone.
  - Gastro-protection - GIT motility.
  - Regulation of renal and reproductive functions.
- PGs and TXA_2 act on specific receptors:
  1. IP receptors for PGI_2 (prostacyclin).
  2. TP receptors for TXA_2.
  3. DP receptors for PGD_2.
  4. FP receptors for $PGF_{2\alpha}$.
  5. EP_1, EP_2 and EP_3 receptors for PGE series.

Physiological Role of PGs	Uses of PG Analogs	Effects of PG Inhibition
1. Role in Inflammation • COX activation is responsible for formation of inflammatory mediators (e.g. PGE_2, PGI_2,) which accompanies tissue injury. • PGE, I_2 & D_2 in acute inflammation potentiate histamine & BK → VD, ↑ capillary permeability, ↑ pain induced by BK.		• **NSAIDs** mediate their analgesic & anti-inflammatory effects by↓ PG synthesis (⊖ cyclooxygyenase) • **Corticosteroids** induce anti-inflammatory effects by ⊖ phospholipase A_2→ ↓ PGs, LTs & PAF.
2. Thermoregulation • PGE generated by endogenous interleukin-1 sets hypothalamic thermostat at a higher level → ↑ temperature in fever.		• Antipyretic effect of **NSAIDs** is due to ⊖ of PGE generation in hypothalamus → reset thermostat.
3. Gastro-protection • PGE → - ↓ Gastric HCl. - ↑ Mucus secretion (but ↑ gastric motility).	• **Misoprostol** (PGE): Given with NSAIDs or steroids to ↓ ulcer risk. • **Lubriprostone** (PGE_1 derivative) →↑ GIT secretions → treatment of constipation.	• The ulcerogenic effects of corticosteroids and NSAIDs are due to inhibition of PGE synthesis in GIT.

Physiological Role of PGs	**Uses of PG Analogs**	**Effects of PG Inhibition**
4. Kidney (PGE) a. VD →↑ renal blood flow. b. Inhibits Na^+ reabsorption. c. ↑ renin secretion.		• **NSAIDs**: ↓ renal PGs → Analgesic nephropathy Na^+ & water retention, Hyperkalemia.
5. Platelet Function: Balance between PGI_2→ inhibits aggregation TXA_2: ↑ aggregation		• Antithrombotic effect of low dose **aspirin** is due to selective ⊖ of platelet TXA_2 synthesis.
6. Vascular Tone • TXA_2 → VC. • PGE & PGI_2 → VD. • Patency of ductus arteriosus depends on PGE_2 and PGI_2.	• **Epoprostenol** (PGI_2) Late stage of pulmonary hypertension (i.v. infusion) • **Treprostinil** (PGI_2): Early stages of pulmonary hypertension (i.v./ s.c./ oral/ inhalation). • **Alprostadil** (PGE_1): Maintains patency of ductus arteriosus in congenital pulmonary stenosis until surgery.	• **Indomethacin** Inhibits PG synthesis → closes patent ductus arteriosus in respiratory distress syndrome (resulting from failure of closure of ductus arteriosus in infants).
7. Ophthalmic: **PGF2α** → ↑ aqueous humor outflow → ↓ IOP in glaucoma	• **Latanoprost (PGF2α):** of choice in simple glaucoma (locally)	

Physiological Role of PGs	Uses of PG Analogs	Effects of PG Inhibition
8. Reproduction **Males**: • PGE → -VD → erection & sperm motility **Females:** • **PGE** → - Cervical ripening - Uterine contractions • **PGF2α**: uterine contractions	• **Alprostadil** (PGE_1): In erectile dysfunction → VD of cavernosal arteries. • **Misoprostol**[7] (PGE): Induction of abortion • **Dinoprostone** (PGE_2): Induces labor/ abortion. • **Carboprost** ($PGF_{2\alpha}$): Induction of abortion	• **NSAIDs** ⊖ PGE & $PGF_{2\alpha}$ synthesis: used to prevent premature labor & dysmenorrhea.
9. Bronchial Tone • **PGI2 - PGE → dilation.** • **PGF2α - PGD2 - TXA2 → bronchospasm.**	• **PGF2α → bronchospasm thus dinoprost is given intra-vaginally &PGE_2 is preferred.**	

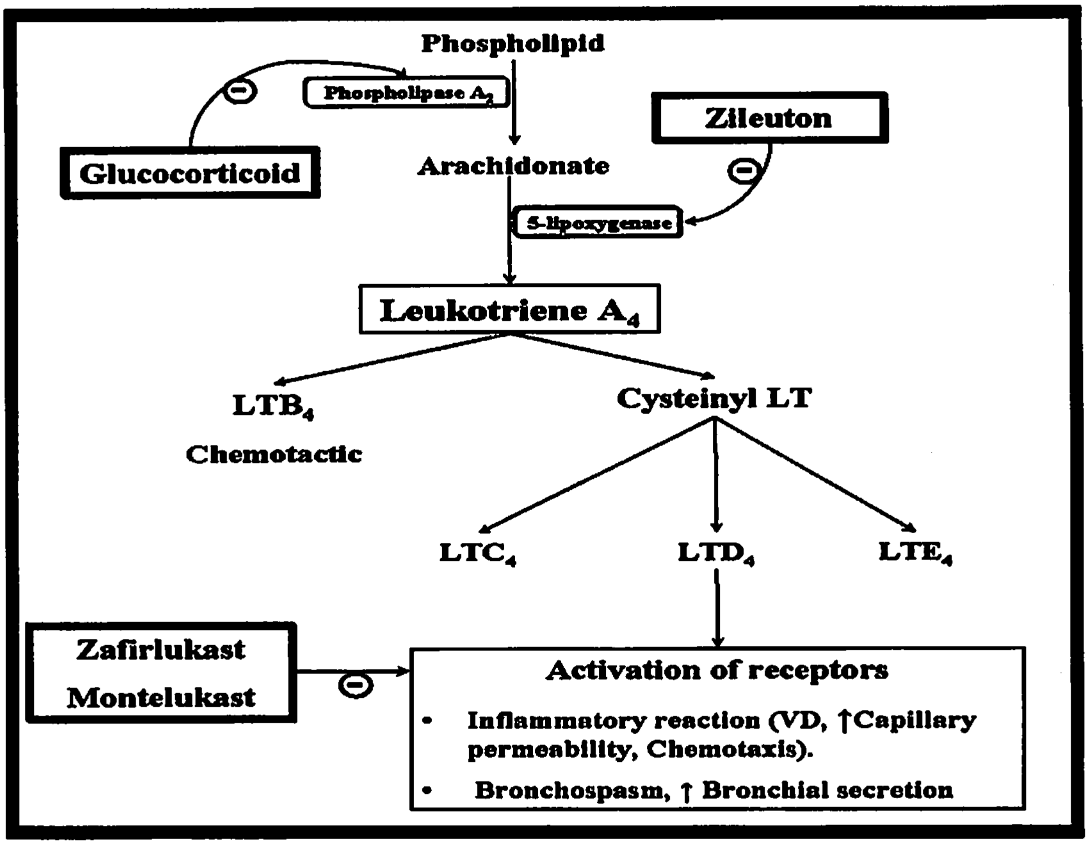
Adverse effects of PG analogs

1. **Latanoprost** → gradual change in iris color – keratopathy - corneal erosion (rare)
2. **Dinoprostone & misoprostol** → diarrhea.
3. **Carboprost** →bronchospasm
4. **Alprostadil** → penile pain, urethral burning, vaginal itching in partner (locally), dizziness & tachycardia (if absorbed systemically).

---

[7] **Misoprostol**: Used for induction of abortion in the 1st trimester (+ mifepristone) and is used alone in the 2nd trimester.

LEUKOTRIENES (LTS)


Phospholipid
Phospholipase A_2
Glucocorticoid
Arachidonate
Zileuton
5-lipoxygenase
Leukotriene A_4
LTB_4
Chemotactic
Cysteinyl LT
LTC_4
LTD_4
LTE_4
Zafirlukast
Montelukast
Activation of receptors
Inflammatory reaction (VD, ↑Capillary permeability, Chemotaxis).
Bronchospasm, ↑ Bronchial secretion

Synthesis: LTs are synthesized from arachidonic acid by lipooxygenase enzyme.

LTs include:

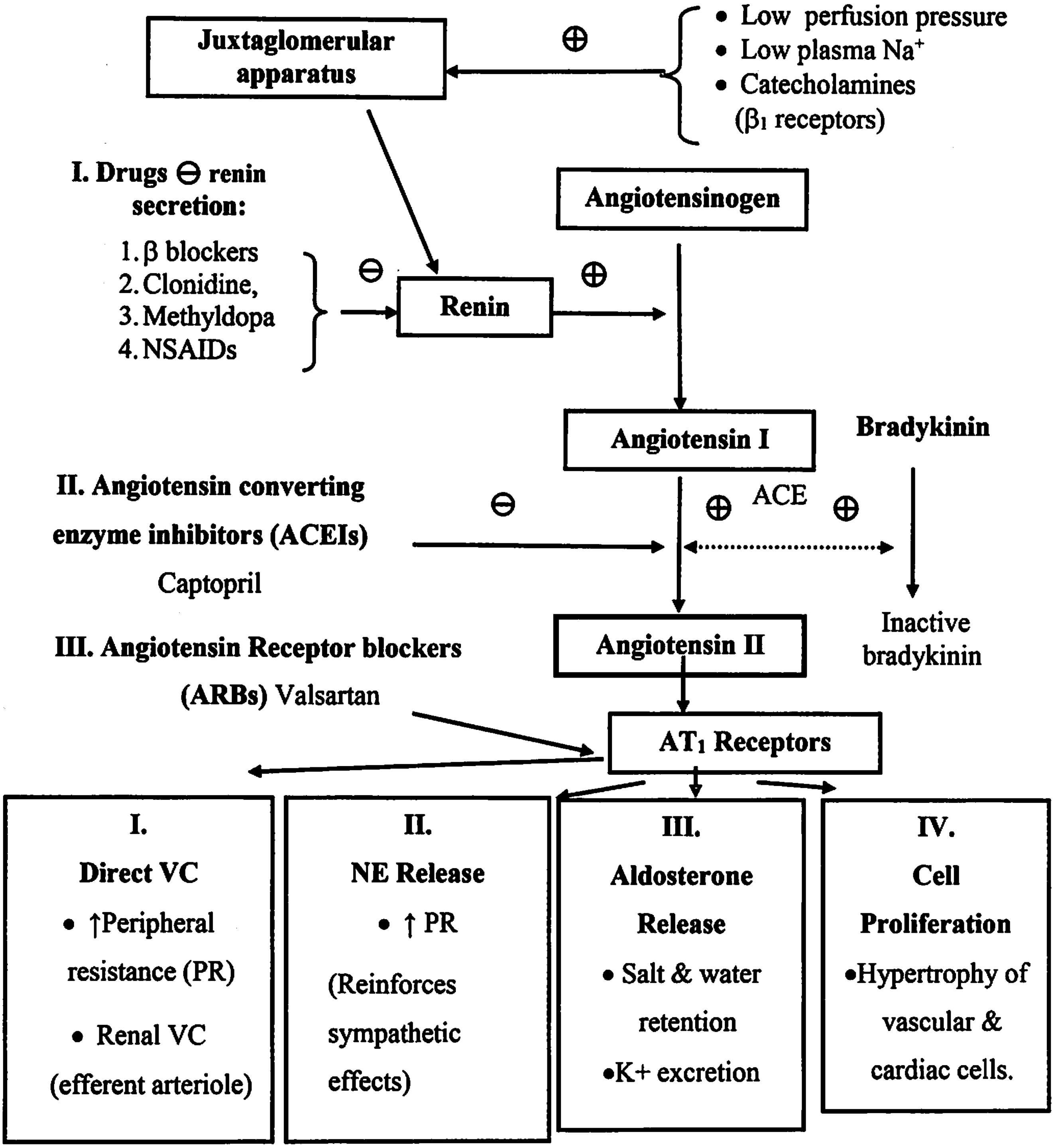
1. LTB_4: powerful chemotactic agent → local accumulation of WBCs.
2. Cysteinyl LTs (LTC_4, D_4 & E_4):
   - Mediators of asthma → potent spasmogens → bronchospasm - ↑ mucus - inflammatory reactions.
   - Present in sputum of patients with asthma, chronic bronchitis & allergic rhinitis.

Inhibitors of LTs include:

1. Lipooxygenase inhibitors: zileuton.
2. LT receptor antagonists: zafirlukast and montelukast.

ANGIOTENSIN II

(Powerful vasopressor)


Juxtaglomerular apparatus
⊕
• Low perfusion pressure
• Low plasma Na⁺
• Catecholamines (β1 receptors)
I. Drugs ⊖ renin secretion:
1. β blockers
2. Clonidine,
3. Methyldopa
4. NSAIDs
⊖
Renin
⊕
Angiotensinogen
Angiotensin I
Bradykinin
II. Angiotensin converting enzyme inhibitors (ACEIs)
Captopril
⊖
⊕
ACE
⊕
Inactive bradykinin
III. Angiotensin Receptor blockers (ARBs) Valsartan
Angiotensin II
AT1 Receptors
I.
Direct VC
• ↑Peripheral resistance (PR)
• Renal VC (efferent arteriole)
II.
NE Release
• ↑ PR
(Reinforces sympathetic effects)
III.
Aldosterone Release
• Salt & water retention
•K+ excretion
IV.
Cell Proliferation
•Hypertrophy of vascular & cardiac cells.

N.B.: ↑ Angiotensin II → feedback inhibition of renin release.

Other Angiotensin II receptors: AT2: vasodilation & antiproliferative - **AT4:** prothrombotic (↑fibrinogen &↑ plasminogen activator inhibitor$_1$).

KININS

- Potent vasodilator peptides formed by action of kininogenases on kininogens.
- They are inactivated by kininase I & II (ACE) which is inhibited by ACEIs.

Mechanism of Action

- **Directly**: on specific receptors: **B_1** receptors; stimulated mainly by Lys-bradykinin & **B_2** receptors; stimulated mainly by bradykinin (BK).
- **Indirectly**: via phospholipase A_2 & liberation of PGs.

Actions of Kinins

- Potent arteriolar dilators, increasing capillary permeability & lowering BP.
- Spasmogenic on uterus and bronchi → bronchospasm and cough.
- Spasmogenic on intestine & ↑ fluid secretion → diarrhea.
- They produce pain and have a role in inflammation and allergy.
- Stimulate nasopharyngeal secretion in allergic rhinitis.

Therapeutic implications

1. Accumulated bradykinin caused by angiotensin converting enzyme inhibitors (ACEIs) → vasodilator and hypotensive actions & cough.
2. NSAIDs mediate part of their analgesic & anti-inflammatory effects by inhibition of PG production induced by BK.

PLATELET-ACTIVATING FACTOR (PAF)

- Active lipid released from most inflammatory cells (neutrophils, macrophages, eosinophils, mast cells, basophils) & platelets.
- Synthesized from phospholipids by phospholipase A_2 → inhibited by **Corticosteroids**

Pathophysiological role of PAF

1. Inflammatory & allergic mediator; chemotaxin to eosinophils in bronchial mucosa.
2. Spasmogenic on bronchial & ileal smooth muscles.
3. Induces platelet aggregation.

Lecture Notes

PHARMACOLOGY

- Renal & CVS
- Blood
- Respiration
- GIT

Volume 2

Pharmacology Department
Faculty of Medicine
Ain Shams University
2019/2020

Lecture Notes

PHARMACOLOGY

Volume 2

- Renal & CVS
- Blood
- Respiration
- GIT

Pharmacology Department
Faculty of Medicine
Ain Shams University
2019/2020

Preface

Pharmacology is an ever-changing medical science. The recent, rapid advances in molecular biology and biotechnology have added relevant information to drug therapy. This edition of "Lecture Notes on Pharmacology" provides the most recent advances in drug therapy within a concise framework.

This work is the result of the combined effort of the Professors of Pharmacology Department; Ain Shams University. "Each of us is unique in their own way. We have something to learn from everyone". Colleagues and students are encouraged to communicate their suggestions. Authors will be pleased to receive comments concerning this edition

Head of Pharmacology Department

Professor Dr. Lobna Bassyouni

2019-2020

Professors of Pharmacology Department

Head of Department

Prof. Dr. Lobna Bassyouni

Prof. Dr. Ahmed Nour Eldin
Prof. Dr. Sahar Kamal

Editorial Board: Prof. Dr. Ahmed Abdel-Salam - Prof. Dr. Olfat Hassan

Authors

Prof. Dr. Zeinab Labib
Prof. Dr. Ahmed Abdel-Salam
Prof. Dr. Olfat Hassan

Prof. Dr. Hoda Sallam
Prof. Dr. Mona Hassan
Prof. Dr. Dr. Sonia Saleeb
Prof. Dr. Osama El Serafy
Prof. Dr. Ahmed Khalil
Prof. Dr. Mohamed Abdel-Bary
Prof. Dr. Ahmed Abedel Tawab
Prof. Dr. Sawsan Abou el Fetouh
Prof. Dr. May Hamza
Ass Prof. Amany Helmy

Deep appreciation for the valuable contribution of

Prof. Dr. Yousria Wahba
Prof. Dr. Samira Mahmoud
Prof. Dr. Adel el Bakry
Prof. Dr. Mahdy Salama
Prof. Dr Sayed Kamel
Prof. Dr. Somia Massoud
Prof. Dr Atef EL-Esawy.
Prof. Dr. Ahmed Badawy

Computer graphics & designs: Dr. Essam Ghazaly - Dr. Mohamed Bahr

CONTENTS

Volume II

1. Renal Pharmacology ....9 - 29

2. Cardiovascular Pharmacology..33 - 87

3. Blood Pharmacology...91 - 126

4. Respiratory Pharmacology 129- 154

5. Gastrointestinal Pharmacology...157- 185

I. RENAL PHARMACOLOGY

Intended Learning Outcomes (ILOs)

By the end of this chapter, the student should be able to:

- List 5 major groups of diuretics & relate them to their sites of action.
- List the major uses & toxicities of thiazides, loop diuretics & potassium sparing diuretics.
- Explain why loop diuretics are used in emergency cases and in edema refractory to other diuretics.
- Explain the differences between the effects of loop diuretics and thiazides on blood electrolytes and how this relates to their therapeutic uses and side effects.
- Explain why spironolactone is of choice in edema of hyperaldosteronism such as liver cirrhosis while thiazides are not favoured.
- Explain why mannitol is contraindicated in renal failure & heart failure.
- Discuss the different causes of refractory edema & their management.
- List the most common causes of disturbances of potassium homeostasis and their management.

RENAL PHARMACOLOGY

Basic Physiology of the Kidney

The kidney performs two major functions:

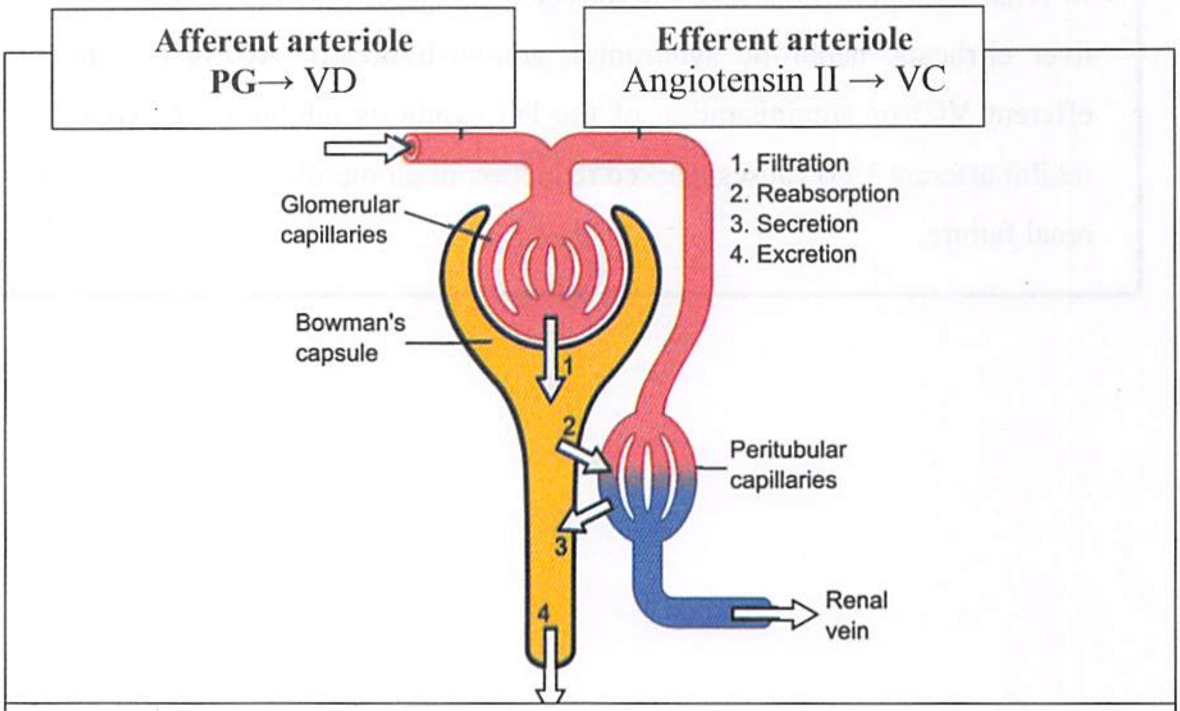
- Excretion of waste products such as urea, creatinine and uric acid.
- Control of blood volume, electrolytes and acid-base balance.

Structure of the Nephron

- The nephron is the functional unit of the kidney. It is formed of a glomerulus, proximal tubule, loop of Henle, distal tubule & collecting duct.

Blood Supply to the Nephron

- The afferent arteriole to the nephron branches to form the glomerular capillary network from which arises the efferent arteriole.
- The efferent arteriole branches to form the peritubular capillary network around the tubules and the loop of Henle


Afferent arteriole
PG→ VD
Efferent arteriole
Angiotensin II → VC
1. Filtration
2. Reabsorption
3. Secretion
4. Excretion
Glomerular capillaries
Bowman's capsule
Peritubular capillaries
Renal vein
1
2
3
4

Maintenance of Glomerular Filtration in Hypoperfusion States

In renal hypoperfusion, glomerular pressure is ↑ to maintain GFR through: ↑ Ag II → VC of efferent arteriole & ↑ PG → VD of afferent arteriole→↑ blood flow .

Maintenance of glomerular filtration in hypoperfusion states

- The juxtaglomerular complex (baroreceptors in the afferent arteriole & chemoreceptors in the macula densa in distal tubules) maintains glomerular filtration during hypoperfusion by the following mechanisms:
  a. In renal hypoperfusion states, low glomerular pressure activates baroreceptors in the afferent arteriole & low NaCl concentration activates chemoreceptors in the macula densa → secretion of renin enzyme →↑Angiotensin II → VC of efferent arteriole →↑ pressure in glomerular capillaries thus maintaining GFR.
  b. Activation of chemoreceptors in the macula densa also stimulates secretion of PGs→ vasodilation of afferent arteriole →↑ blood flow & glomerular pressure thus maintaining GFR.

- In renal hypoperfusion states (hypovolemia, diuretic therapy, heart failure, liver cirrhosis, nephrotic syndrome), administration of ACEIs (→ inhibit efferent VC) or administration of the PG synthesis inhibitors NSAIDs (→ inhibit afferent VD) causes marked reduction in glomerular filtration → acute renal failure.

Transport of Water & Electrolytes in the Nephron

- The main function of the kidney is to excrete waste products such as urea & creatinine which are filtered in the glomeruli & not reabsorbed.
- Following glomerular filtration, most of the important blood constituents are reabsorbed in the different segments of the nephron as follows:

1. Proximal Tubules

- 60% of filtered Na^+ is reabsorbed as NaCl (Na^+ is actively reabsorbed by Na^+-pump, Cl^- follows Na^+ passively).
- 5% of filtered Na^+ is reabsorbed as $NaHCO_3$ in exchange with H^+ under effect of carbonic anhydrase enzyme to preserve blood $NaHCO_3$.
- Ca^{2+}, Mg^{2+} and K^+ reabsorption follows that of Na^+ to the same degree.
- Water is reabsorbed passively (proximal tubules, highly water permeable).
- Glucose & amino acids are reabsorbed by Na^+ cotransport mechanism.
- Mannitol & sucrose are not reabsorbed → excreted as such in urine retaining water (→ used as osmotic diuretics).

2. Thick Ascending Loop of Henle

- 25% - 30% of filtered Na^+ is reabsorbed via active 2 $Cl^-/Na^+/K^+$ pump.
- This segment is impermeable to water rendering the tubular fluid hypotonic (diluting segment).
- **Medullary hypertonicity**: is created by active reabsorption of Na^+ coupled with passive transport of urea at this segment. It provides osmotic driving forces for water reabsorption from collecting tubules under the effect of ADH to conserve body water & concentrate urine. Renal PGs interfere with medullary hypertonicity by inhibiting Na^+ reabsorption → diuresis.

3. Distal Tubules (including collecting duct)

- **Early Part of Distal Tubule** (diluting Segment): Continuation of the thick ascending loop of Henle. Impermeable to water. There is active NaCl reabsorption (10%).

More Distal

- Na^+ (5%) is reabsorbed in exchange with K^+ or H^+ via $Na^+/K^+/H^+$ pump...
- Na^+ reabsorption is partly dependent on aldosterone & partly independent.

Collecting Duct

- ADH increases the permeability of the collecting duct to water which is reabsorbed by the driving osmotic force of the hypertonic medulla.

DIURETICS

- Diuretics are drugs that cause a net loss of sodium and water from the body through the kidney resulting in contraction of the extracellular fluid.

They include:

A. **K^+-losing diuretics**

- Loop diuretics.
- Thiazides.
- Osmotic diuretics.
- Carbonic anhydrase inhibitors.

B. **K^+-sparing diuretics**

- Spironolactone - amiloride - triamterene.

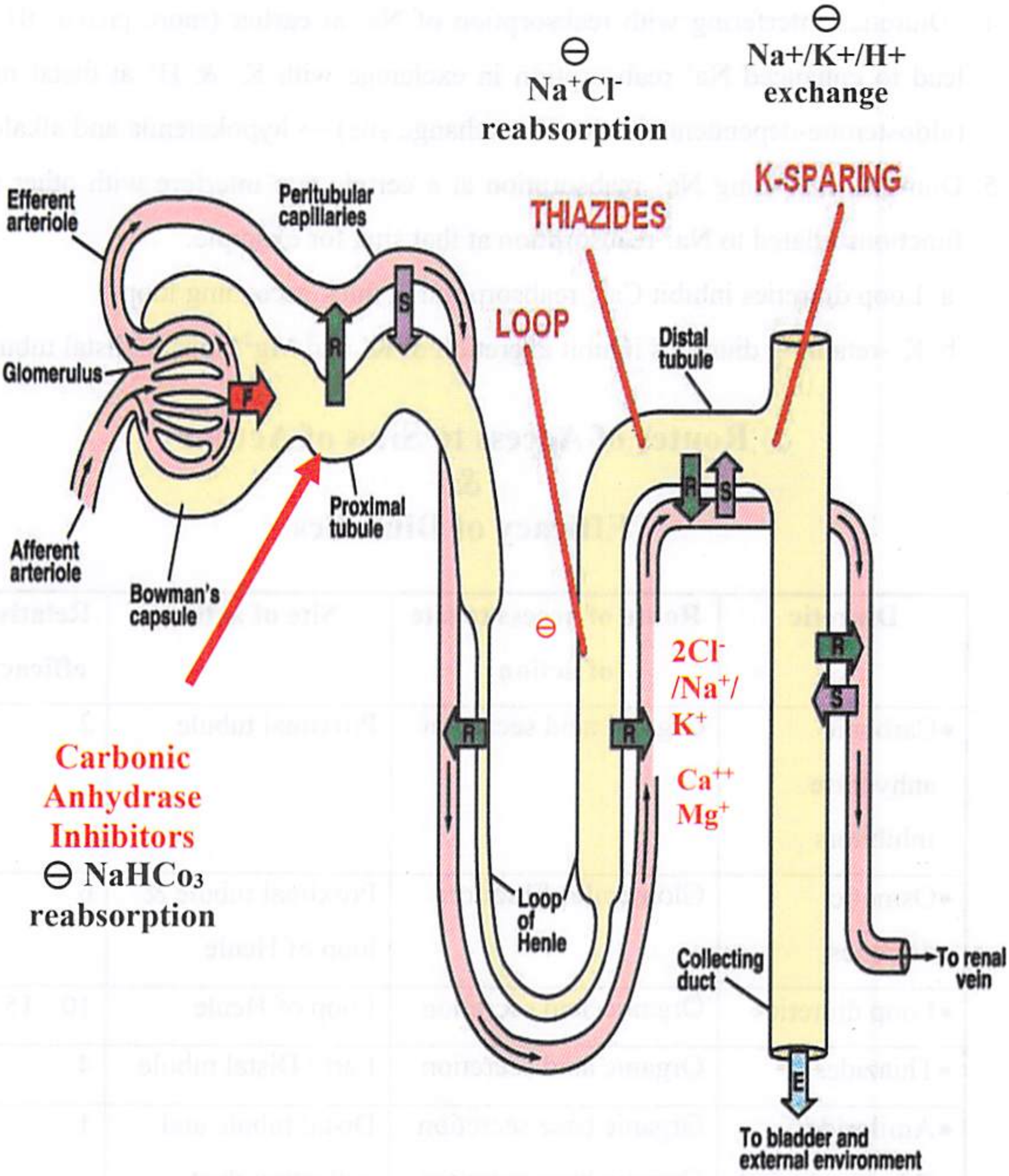
General Principles in Diuretic Therapy

1. Diuretics act by different mechanisms and at different sites along the nephron (see table). Thus, they have a synergistic effect if they are combined together.
2. All diuretics (except spironolactone) have to reach their site of action in the lumen of the nephron, by organic acid or organic base secretory systems (see table). Therefore, any defect in delivery of diuretics to their sites of action (e.g. in renal impairment) will result in diminished diuretic response.
3. Carbonic anhydrase inhibitors, thiazides and loop diuretics are organic acids secreted by organic acid secretory systems and, therefore, compete with secretion of other organic acids such as uric acid resulting in hyperuricemia.

4. Diuretics interfering with reabsorption of Na^+ at earlier (more proximal) sites lead to enhanced Na^+ reabsorption in exchange with K^+ & H^+ at distal tubule (aldosterone-dependent $Na^+/K^+/H^+$ exchange site) → hypokalemia and alkalosis.
5. Diuretics inhibiting Na^+ reabsorption at a certain site interfere with other renal functions related to Na^+ reabsorption at that site, for example:
   a. Loop diuretics inhibit Ca^{2+} reabsorption at thick ascending loop.
   b. K^+-retaining diuretics inhibit excretion of K^+ and Mg^{2+} ions in distal tubule.

Routes of Access to Sites of Action
&
Efficacy of Diuretics

Diuretic	Route of access to site of action	Site of action	Relative efficacy
• Carbonic anhydrase Inhibitors	Organic acid secretion	Proximal tubule	2
• Osmotic diuretics	Glomerular filtration	Proximal tubule & loop of Henle	6
• Loop diuretics	Organic acid secretion	Loop of Henle	10 - 15
• Thiazides	Organic acid secretion	Early Distal tubule	4
• Amiloride • Triamterene • Spironolactone	Organic base secretion Organic base secretion Peritubular circulation	Distal tubule and collecting duct	1


⊖
Na^+Cl^-
reabsorption
⊖
Na+/K+/H+
exchange
K-SPARING
THIAZIDES
LOOP
Efferent arteriole
Peritubular capillaries
Glomerulus
F
R
S
Distal tubule
Proximal tubule
Afferent arteriole
Bowman's capsule
⊖
$2Cl^-$
$/Na^+/$
K^+
Ca^{++}
Mg^+
Carbonic Anhydrase Inhibitors
⊖ $NaHCO_3$
reabsorption
Loop of Henle
Collecting duct
To renal vein
E
To bladder and external environment

Sites of Action of Diuretics

LOOP DIURETICS

(High ceiling[1] - most effective diuretics)

Frusemide- Bumetanide- Torsemide

Mechanism of action

1. Block 2 $Cl^-/Na^+/K^+$ reabsorption in thick ascending loop of Henle resulting in:
   - Excretion of 20% of filtered Na^+.
   - Interference with medullary hypertonicity → failure of water reabsorption by medulla under effect of ADH → excretion of water in excess of Na^+.
2. Release vasodilator PGs which intensify the action of loop diuretics through:
   - VD of **Afferent** arteriole → ↑ glomerular filtration.
   - Inhibiting Na^+ reabsorption at the ascending loop of Henle.

   N.B: NSAIDs inhibit PG synthesis → interfere with action of loop diuretics.

Other actions

i. **Venodilator action** → adds to their benefits in acute pulmonary oedema.

ii. **Increase renal blood flow**→ useful in acute renal failure.

Pharmacokinetics (in healthy subjects)

- **Frusemide** absorption is variable 10-100% (average 50%)→ try different doses before considering drug ineffective.
- **Bumetanide & torsemide** are nearly completely absorbed → do not require dose adjustment on switching from oral to IV.
- Loop diuretics are highly bound to plasma protein (90%).

---

[1] Loop diuretics are high ceiling diuretics as they block nearly all reabsorption sites → excretion of 20% of filtered Na^+ (maximum capacity of the ascending loop).

Indications of loop diuretics

I. **Emergency cases** (as it is rapid with potent dehydrating effect; can be given IV)

1. Hypertensive encephalopathy.
2. Acute pulmonary edema (**Venodilation**).

II. Cases refractory to other Diuretics

1. Refractory edema of severe CHF & renal insufficiency.
2. Refractory edema of liver cirrhosis (added to full dose of spironolactone).
3. Acute renal failure (**↑renal blood flow**).

III. Electrolyte& Acid-base Disturbances

1. **Hypercalcemia:** added to IV saline[2].
2. **Hyperkalemia**:
   - Inhibit K^+ reabsorption in loop of Henle & increase K^+ excretion in exchange with Na^+ in distal tubules.
3. **Dilutional hyponatremia**:
   - ↑ water excretion more than Na^+.
4. **Distal renal tubular acidosis:**
   - ↑ H^+ excretion in exchange with Na^+ at distal tubule.

Doses and Preparations

- **Frusemide:** oral dose 80 mg (40 - 120); IV dose 40 mg (20 - 60 mg).
- **Bumetanide** (40 times more potent): oral and IV dose 1 - 5 mg.
- **Torsemide** (10 -100 mg)

---

[2] In hypercalcemia IV saline may be sufficient alone for Ca^{2+} excretion as it corrects the hypoperfusion responsible for ↓ GFR & ↑ tubular Ca^{2+} reabsorption.
Loop diuretics are added if necessary → inhibit Ca^{2+} reabsorption in loop of henle.

Adverse Effects

I. Metabolic & electrolyte disturbances

1. Hypovolemia - hypotension - collapse - hemoconcentration & thrombosis (due to intensive diuresis in a short time).
2. Hypokalemia & alkalosis: ↑ Na$^+$ delivered to distal tubules → excretion of K$^+$ & H$^+$ in exchange with Na$^+$ by aldosterone (avoided by adding spironolactone).
3. Hypomagnesemia. } Inhibit reabsorption in loop of Henle
4. Hypocalcemia
5. Hyperuricemia (compete with uric acid for organic acid secretory system).

II. Other Adverse Effects

1. Ototoxicity (especially with aminoglycosides).
2. Interstitial nephritis (especially with cephalosporins).
3. Myalgia (bumetanide).
4. Sulfonamides-hypersensitivity[3].
5. Refractoriness (see below).

Causes of refractoriness to loop diuretics & its management

A. Pharmacokinetic Causes

I. Defective intestinal absorption in decompensated HF:

Treatment: Give the diuretic IV.

II. Defective pp binding in hypoalbuminemic states (liver cirrhosis & nephrotic syndrome) → extravascular diffusion of diuretic →↓ renal excretion:

Treatment: Mix the diuretic with albumin prior to infusion.

III. Defective excretion of diuretics by acid secretory system in renal impairment due to accumulation of acids:

Treatment: ↑ Dose of frusemide to 5 folds.

---

[3] In patients with sulfonamide allergy the loop diuretic ethacrynic acid may be used.

B. Pharmacodynamic Causes

I. Hypertrophy of distal tubular cells (on chronic use →↑ Na$^+$ reabsorption → blunts the action of the diuretic):

Treatment: Add thiazides to inhibit Na$^+$ reabsorption in distal tubules & amplify the effect of loop diuretics.

II. Na$^+$ lost by loop diuretic is reabsorbed in exchange with K$^+$ in distal tubules (under the effect of aldosterone):

Treatment: Add the aldosterone antagonist spironolactone.

THIAZIDE DIURETICS

(Moderately powerful [low-ceiling] diuretics)

Mechanism of Action

- Inhibit active electroneutral NaCl reabsorption in the early part of distal tubule (diluting segment) causing excretion of 5-10 % of filtered Na^+.

Vasodilator action

- This is the basis for their antihypertensive effect.

Therapeutic Uses

I. CVS

1. **Hypertension**
   - Initially: diuresis → ↓ blood volume.
   - Persistent effect: due to vasodilation.
2. **CHF**
   - To overcome refractoriness to loop diuretics.

II. Renal

1. **Nephrogenic diabetes insipidus**
   - Chronic therapy paradoxically decreases urine output in nephrogenic diabetes insipidus (may be due to ↓ PG → ↓ GFR → ↓ urine volume).
2. **Idiopathic hypercalciuria & Ca^{2+} stones**
   - Chronic therapy → ↓ GFR & ↑ tubular Ca^{2+} reabsorption → ↓ Ca^{2+} excretion.

N.B.:

- Patients on thiazides have a reduced risk of osteoporosis & hip fractures as they ↓ Ca^{2+} excretion → thiazides are preferred in elderly hypertensives.
- Effectiveness of thiazides is reduced in renal impairment → **metolazone** (thiazide like preparation) is effective in impaired renal function.

Adverse Effects

1. Hypokalemia[4] & metabolic alkalosis, with ↑ risk of hepatic encephalopathy in liver impairment[5].
2. Hyponatremia & hypomagnesemia.
3. Glucose intolerance[6].
4. Hyperlipidemia: ↑ LDL & ↓ HDL → coronary sclerosis.
5. Hyperuricemia.
6. Hypersensitivity.
7. Impotence.

Doses and Preparations

- Hydrochlorthiazide (short acting < 24 h): 25 mg 2 - 4 times/d.

Drugs related to Thiazides (long acting >24 h)

- Chlorthalidone: 100 mg.
- Indapamide: 2.5 mg once/d in hypertension, less metabolic side effects.
- Metolazone: effective in impaired renal function

---

[4] More common with thiazides than with loop diuretics because part of delivered Na^+ by loop diuretics is reabsorbed by thiazide area before reaching the area of Na^+-K^+ exchange.

[5] Hepatic encephalopathy in patients with liver impairment is due to alkalosis induced by thiazides, which →↑ lipid-soluble NH_3 rather than water-soluble easily excreted NH_4^+. Accumulation of NH_3, due to failure of liver to convert it to urea→ its diffusion into brain depleting excitatory glutamic acid → coma.

[6] Thiazide-induced hypokalemia → ↑ K^+ outflux from pancreatic islet cells → membrane hyperpolarization → ⊖ Ca^{2+} influx → ⊖ insulin release.

POTASSIUM-RETAINING DIURETICS

(Weak diuretics; excrete only 5% of Na+ filtrate)

Mechanism

Inhibit $Na^+/K^+/H^+$ exchange at the distal tubule by two different mechanisms:

I. Indirect: Spironolactone & eplerenone (delayed onset of action)

- Antagonize aldosterone receptor-binding resulting in decreased synthesis of a specific protein that stimulates the Na^+ pump (requires 3 - 4 days).

II. Direct: Triamterene & amiloride (rapid onset of action)

- Act independent of aldosterone → block Na^+ channels directly.

Indications

1. In CHF

- Spironolactone added to loop diuretics & ACEIs→↓ mortality by 30%,

2. Edema of hyperaldosteronism

- Spironolactone is of choice: more effective[7].

3. Hypokalemia and hypomagnesemia

- Triamterene and amiloride, are preferable to spironolactone as they are more rapid & shorter acting → daily dosage adjustment possible.
- They are combined with K^+-losing diuretics (loop & thiazide diuretics) to potentiate their diuretic effect & to antagonize their hypokalemic effect (more effective than exogenous K^+ & Mg^{++} supplements).

Adverse Effects

1. Hyperkalemia & metabolic acidosis.
2. Gynecomastia: due to antiandrogenic effect of spironolactone.

---

[7] Edema of hyperaldosteronism (liver cirrhosis, nephrotic syndrome & CHF) is resistant to other diuretics since Na^+ lost by other diuretics is reabsorbed again by excess aldosterone at $Na^+/K^+/H^+$ exchange site in distal tubule (also directly acting K^+-retaining diuretics are less effective than spironolactone in hyperaldosteronism.

OSMOTIC DIURETICS

(MANNITOL)

(Powerful diuretic action)

Mechanism of Action

Mannitol is freely filtrated at the glomerulus with limited reabsorption by renal tubules resulting in:

- Increase in osmotic pressure of tubular filtrate with retention of water and increased urine volume (main effect → useful as dehydrating agents).
- The high osmotic pressure of tubular filtrate opposing plasma osmotic pressure inhibits Na^+ reabsorption throughout the nephron but to a much lesser extent than water (so, they are ineffective in edematous states with Na^+ overload).

Indications

1. **Dehydrating agents for:**
    - a. Rapid reduction of intracranial tension in cerebral edema caused by head injury or brain surgery.
    - b. Rapid reduction of intraocular tension in acute congestive glaucoma.
2. **Prophylaxis against acute renal failure:**
    - Mannitol prevents acute renal failure following surgery, trauma or hemolytic transfusion reactions by maintaining high rate of urine flow, preventing concentration of toxic agents which cause renal damage.

Adverse Effects & Contraindications

- In impaired renal function (e.g. acute renal failure), mannitol is not filtered & persists in plasma → ↑ intravascular volume → heart failure & dilutional hyponatremia→ **CI in acute renal failure & congestive heart failure.**

CARBONIC ANHYDRASE INHIBITORS (CAIs)

Acetazolamide – brinzolamide - dorzolamide

Mechanism of Action

- Inhibit carbonic anhydrase enzyme responsible for H^+ production → inhibition of Na^+/H^+ exchange at the proximal tubules→ inhibition of $NaHCO_3$ reabsorption → loss of $NaHCO_3$ in urine leading to:
  - **a.** Diuresis with alkaline urine.
  - **b.** Decreased blood bicarbonate with metabolic acidosis.

N.B.: CAIs are weak diuretics as most of the fluid & Na^+ lost are reabsorbed at more distal nephron sites.

Indications

1. Emphysema and high altitude sickness (correct alkalosis by inducing metabolic acidosis).
2. Epilepsy: suppress the irritable focus directly or by inducing acidosis.
3. Eye: treatment of glaucoma by decreasing formation of aqueous humor [Methazolamide is preferred (less renal & systemic effects)].
4. Excretion of of acidic toxins as salicylates & barbiturates (alkalinize urine).

Adverse Reactions

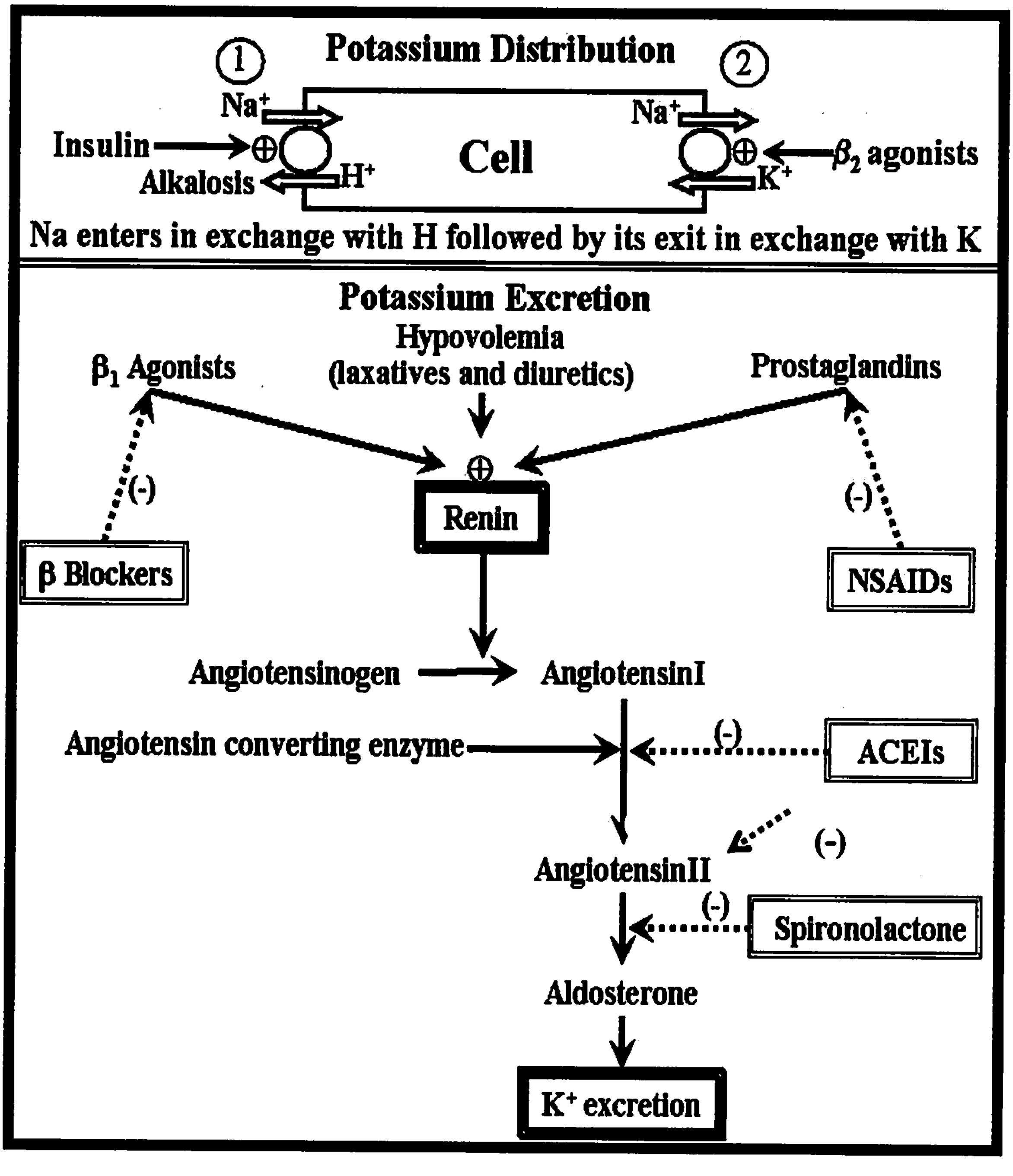
- Metabolic acidosis → drowsiness & refractoriness to the diuretic effect[8].
- Calcium and phosphate stones due to alkaline urine.
- Hypersensitivity reactions as they are sulfonamide derivatives.

---

[8] The body preseves $NaHCO_3$ to buffer acidosis.

DRUGS AND POTASSIUM HOMEOSTASIS

- K^+ is the major intracellular cation with low concentration in the extracellular fluids (3.5 - 5 mEq/l). The body maintains this low plasma K^+ level through:
  - i. Promoting entry of K^+ into the cell by the Na^+-K^+ ATPase pump. Insulin & β_2 adrenergic receptor stimulation activate this pump.
  - ii. K^+ excretion through kidney (mainly) & colon (limited amount). Both are stimulated by aldosterone through the renin-angiotensin system.


Potassium Distribution
①
②
Na+
Insulin
⊕
Alkalosis
H+
Cell
Na+
⊕
K+
β2 agonists
Na enters in exchange with H followed by its exit in exchange with K
Potassium Excretion
Hypovolemia
(laxatives and diuretics)
β1 Agonists
Prostaglandins
⊕
(-)
(-)
Renin
β Blockers
NSAIDs
Angiotensinogen
AngiotensinI
Angiotensin converting enzyme
(-)
ACEIs
(-)
AngiotensinII
(-)
Spironolactone
Aldosterone
K+ excretion

DISTURBANCES IN K^+ SERUM LEVEL

Causes of Hypokalemia & Hyperkalemia

(See figure)

Hypokalemia	Hyperkalemia
A. Increased K^+ entry into cells: 1. **Insulin** (large dose in ketoacidosis). 2. **↑ CA in stress (β_2 agonist)** 3. **Alkalosis** (due to K^+-losing diuretics or vomiting)[9].	**A. Increased K^+ exit out of cells:** 1. **Digitalis** (⊖ Na^+-K^+ ATPase) 2. **β blockers** (β_2- blockade) 3. **Acidosis** (due to K^+-retaining diuretics & salicylates)[10] 4. **Succinylcholine** (partial depolarization→ K^+ outflux).
B. Increased K^+ loss: 1. **Renal loss:** • Hyperaldosteronism • K^+-losing diuretics as loop diuretics & thiazides. • Liquorice. 2. **Extra-renal loss:** • Laxatives – severe diarrhea.	**B. Defective renal K^+ excretion:** 1. Impaired renal function. 2. **Hypoaldosteronism:** • K^+-retaining diuretics: antagonize aldosterone action. • β_1Bs – NSAIDs: ⊖ renin release. • ACEIs: ↓ Ag II & aldosterone. • ARBs: block AgII receptor

---

[9] H^+ diffuses out of cell to buffer the alkalosis → K^+ diffusion into cells to maintain electronegativity inside the cell.

[10] H^+ diffuses into cell to buffer the acidosis→ K^+ diffusion out of cell to maintain cell electronegativity .

Hypokalemia

Causes: see table

To minimize or correct hypokalemia

1. Use K^+- rich diet as banana.
2. Combine K^+-sparing diuretics with K^+-losing diuretics.
3. Drug holiday for patients taking K^+-losing diuretics.
4. Administer KCl.

N.B.:

- Oral K^+ has gastric & esophageal irritant effect and should be given with plenty of fluids while sitting upright.
- IV potassium may cause phlebitis and should be given in large veins.

Hyperkalemia

(Life threatening condition due to fatal arrhythmias)

Causes: see table

Treatment: according to K^+ level & ECG changes

1. **IV Ca^{2+}**:

   It is the most rapid treatment used in severe cases. It stabilizes myocardial membrane by opposing the effect of hyperkalemia on membrane potential.

2. **Increasing K^+ movement into the cells**:
   - a. **Insulin**: small dose (6 - 8 units) + glucose (20 g IV) to avoid hypoglycemia. IV glucose which stimulates insulin release is preferred.
   - b. B_2 agonist nebulizer (salbutamol).
   - c. **IV sodium bicarbonate**: induces alkalosis which increases influx of K^+[11]

3. **Removal of K^+ from body**:
   - a. Loop diuretics.
   - b. Cation-exchange resins inhibit intestinal absorption of K^+.
   - c. Dialysis in severe resistant cases.

---

[11] Excess alkalinization may inhibit ionization of Ca^{2+} aggravating the effect of hyperkalemia on membrane potential.

Magnesium

- Magnesium is the second most abundant intracellular cation.

Mechanism of action[12]:

- Natural physiologic competitive Ca antagonist at L - calcium channels.
- Antagonist of NMDA glutamate receptors: analgesic, anticonvulsant, and sedative properties.
- Interferes with acetylcholine release: muscle relaxation.
- Decreases release of catecholamines after sympathetic stimulus.

Indications:

1. Torsades de pointes[13] & digitalis induced arrhythmias (Mg sulfate IV; inhibits Ca entry)
2. Hypomagnesemia associated with myocardial infarction[14].
3, Refractory hypokalemia secondary to hypomagnesemia.
4. Constipation: osmotic laxative (Mg sulfate, MgO, milk of magnesia).
5. Antacids.
6. Seizures in preeclampsia (anticonvulsant) – premature labor.
7. **Adjuvant in anesthesia**:
    - Analgesic[15], sedative.
    - ↓Blood pressure response to tracheal intubation[16].
    - Inhibits Ach release at NMJ, potentiates competitive neuromuscular blockers.
8. Severe asthma attacks[17].
9. Diabetic coma and diabetic patients.
10. Muscular pain relief 'Epsom bath salts', gel or in solution topically.

---

[12] As a cofactor, it is involved in more than 300 known reactions, flow of transmembrane ions, muscle contraction, neuronal activity, vasomotor tone, cardiac excitability, etc,....

[13] Mg replaces Ca ion influx into the cell→ ↓ QT interval and relieves torsade de pointes.

[14] During acute myocardial infarction, 80% of patients develop hypomagnesemia in the first 48 hrs, due to ↑ catecholamines[6]. Hypomagnesemia →depolarization → tachycardia[6]

[15] Analgesic effect is due to blockade of NMDA receptors & ↓catecholamines release.

[16] Due to a reduction in the release of catecholamines after sympathetic stimulation.

[17] Inhibits histamine & Ach release, potentiates beta-agonists. Less benefit in moderate asthma.

Adverse effects:

- Diarrhea.
- Drowsiness.
- Hypotension.
- Asystole (with rapid IV administration).
- Teratogenic: category D (fetal skeletal abnormalities).

Hypomagnesemia[18]

- Hypomagnesemia is associated with:
  - Refractory hypokalemia.
  - Cardiac arrhythmia.
  - Heart attacks due to coronary spasm.
  - Seizures, and psychosis.

Predisposing factors for hypomagnesemia

- Diarrhea.
- Diabetes.
- **Drug- induced** (↑ renal excretion)
  - Diuretics[19] - Digitalis.
  - Aminoglycosides - Amphotericin B.

Routes of administration

- Orally: e.g., laxatives, antacids.
- Intravenously: e.g., anticonvulsant in preeclampsia , anti-arrrhythmic.

Preparations

- Mg sulfate - Mg gluconate.
- Mg citrate- Mg oxide- Mg hydroxide (milk of magnesia).
- Mg trisilicate.

---

[18] Hypomagnesemia is seen in 60% of patients in ICU, 7% of admissions for ketoacidosis, & 70% after coronary revascularization.

[19] Diuretics, specially chronic furosemide therapy, are the leading cause of hypomagnesemia.

TREATMENT OF IDIOPATHIC HYPERCALCIURIA

(Common cause of calcium stones)

1. Low dietary Na^+.

2. Thiazides (chronic use).

} ↓ blood volume → ↓ GFR & ↑ tubular Ca^{2+} reabsorption

3. Avoid restriction of dietary Ca^{2+}:

Oral Ca^{2+} binds with oxalate in the intestine decreasing oxalate absorption → ↓ urine oxalate. The low oxalate in urine prevents the formation of Ca^{2+} oxalate stones.

4. Avoid high protein diet:

Proteins produce acidosis which increases Ca^{2+} stones by the following:

1. Acids mobilize calcium from bone to blood and then to urine.
2. Intracellular acidosis consumes citrate decreasing its concentration in blood & urine (urinary citrate normally prevents crystallization of Ca^{2+} stone).

5. Avoid hypokalemia:

Avoid hypokalemia by giving K^+ citrate: hypokalemia is associated with increased intracellular acidosis which decreases citrate excretion in urine.

II. CARDIOVASCULAR PHARMACOLOGY

Intended Learning Outcomes (ILOs)

Antianginal drugs: By the end of this chapter, the student should be able to:

- Recognize the importance of the routine use of aspirin and statins in reducing the risk of ischemic heart disease.
- List the 3 major groups of antianginal drugs & their antianginal mechanisms.
- Discuss the importance of β Bs as 1st choice maintenance therapy of classic angina & why calcium channel blockers (CCBs) are preferred in vasospastic type.
- Differentiate between preparations of nitrates used for relieve of acute anginal attack and those used for maintenance therapy.
- Differentiate between the effects of the 2 main groups of CCBs on the cardiovascular system and how this relates to their uses and side effects.
- Point out the therapeutic uses of CCBs that are shared with beta blockers and those in which beta blockers are contraindicated.

Drugs used in heart failure: By the end of this chapter, the student should be able to:

- Outline the pathophysiology of HF & the role of sympathetic & renin angiotensin system activation as initial compensatory mechanisms & their role in the increase in cardiac loads & further deterioration of myocardial contractility in later stages.
- List drugs that are used to reduce preload, afterload & myocardial contractility in CHF versus those used in acute heart failure.
- Discuss the beneficial effects of β Bs & spironolactone in reducing mortality in HF.
- Explain the beneficial effects of digoxin in HF with atrial fibrillation & why it is no longer considered a first line drug in CHF.
- Explain how the increase in intracellular sodium & calcium are responsible for both the beneficial effects of digoxin on myocardial contractility as well as for its electrophysiological & arrhythmogenic effects.

Antihypertensive drugs: By the end of this chapter, the student should be able to:

- List the major groups of drugs used as monotherapy in hypertension.
- Discuss the choices of different antihypertensive drugs in different disease states.
- Explain why vasodilators such as ACEIs & ARBs are preferred to hydralazine.
- Explain why nitroprusside is only used in severe cases of hypertension .
- Explain why low dose thiazides is preferred to high dose therapy.
- Discuss why the indications of labetalol and esmolol differ from those of bisoprolol in management of hypertension.
- Explain the main differences between ACEIs and ARBs and why they are preferred in diabetics and in patients with nephropathy.
- Compare between the effects of different antihypertensives on heart rate.
- Discuss the beneficial effects of combinations of antihypertensives.

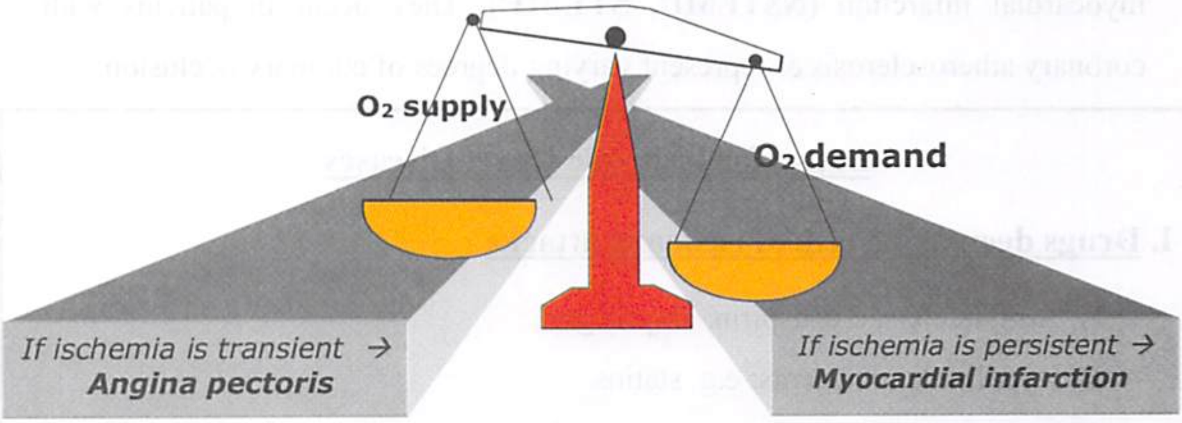
Antiarrhythmic Drugs: By the end of this chapter, the student should be able to:

- Classify antiarrhythmic drugs according to their electrophysiological effects.
- Discuss the choices of different antiarrhythmic drugs in various types of arrhythmias.

CARDIOVASCULAR PHARMACOLOGY

DRUG THERAPY OF ISCHEMIC HEART DISEASES

- Cardiac ischemia results from an imbalance between myocardial O_2 supply & oxygen demand.


O₂ supply
O₂ demand
If ischemia is transient → Angina pectoris
If ischemia is persistent → Myocardial infarction

Classic Angina

- Results when the work done by the heart is increased while the narrow **atherosclerotic coronaries** fail to dilate & increase blood flow to meet the increase in myocardial O_2 demand.
- Presents as anginal pain[1] associated with transient ST segment depression.
- It usually occurs on exertion → so also called exertion or effort angina. It is relieved by rest or nitroglycerin.

Prinzmetal's Variant Angina[2]

- Results from a reversible **coronary vasospasm** with normal O_2 needs→ so also called vasospastic angina.
- Presents as anginal pain associated with transient ST segment elevation or paradoxical T wave normalization.

---

[1] Anginal pain is a sudden pressing chest pain radiating to the neck, jaw, shoulder, & arm, caused by accumulation of metabolites in cardiac muscle.

[2] Named variant as it occurs after variable levels of exertion even at rest & Prinzmetal after the 1st person who described it.

Unstable angina:

Results when an atheromatous plaque ruptures & a **nonocclusive thrombus** is formed which partially occludes the coronary artery producing symptoms of ischemia which are prolonged & may occur at rest (no ↑in serum markers).

Acute coronary syndromes[3]

These syndromes include a group of conditions ranging from unstable angina to myocardial infarction (**NSTEMI**[4], **STEMI**[5]). They occur in patients with coronary atherosclerosis & represent varying degrees of coronary occlusion.

Drugs for Ischemic Heart Diseases

I. Drugs decreasing risk of ischemic attacks

A. Antiplatelets: e.g. aspirin, clopidogrel.
B. Hypolipidemic agents: e.g. statins.
C. Angiotensin converting enzyme inhibitors.

II. Antianginal Drugs

A. Organic Nitrates.
B. Beta adrenoceptor Blockers.
C. Calcium Channel Blockers.
D. **Others**:
  i. Trimetazidine.
  ii. Ivabradine.
  iii. Ranolazine.

---

[3] In some classifications acute coronary syndromes also include classic & Prinzmetal's angina.

[4] Non ST elevation myocardial infarction: Occurs when an intermittently occlusive thrombus causes myocardial necrosis (↑ in serum markers) but collaterals maintain partial viability of myocardium (non ST elevation, non Q wave). ↑ In serum markers (troponin I & T or CK-MB) may not be detectable for hours after presentation, thus it is initially indistinguishable from unstable angina.

[5] ST elevation myocardial infarction: Occurs if the thrombus occludes the coronary vessel & the prolonged ischemia results in myocardial damage with ↑ in serum markers plus ECG changes (ST elevation, Q wave.). Presents with more severe & persistent pain after nitroglycerin.

A. Organic Nitrates

Molecular Mechanism of Action

- Nitrates bind to special receptors on vessel wall. Nitrates release NO which is converted by an SH-dependent enzyme into S-nitrosothiol.
- S-nitrosothiol activates guanyl cyclase → ↑c-GMP →↓ intracellular Ca^{++} → smooth muscle relaxation (e.g. vasodilation; selective venodilators).

Pharmacological actions

I. Relaxation of Vascular Smooth muscles

- Venulodilators → ↓ venous return; ↓ preload.
- Arteriodilators (in higher dose) → ↓ peripheral resistance; ↓afterload.

II. Brief relaxation of other Smooth muscles

Relaxation of GIT smooth muscles; especially:

- Sphincter of Oddi.
- Cardiac opening of oesophagus.

Mechanism of antianginal effect

A. ↓ O_2 demand (relieve pain): **↓ work done by heart through:**

- Venular dilators → ↓ venous return; ↓ preload.
- Arteriolar dilators (in higher dose) → ↓ peripheral resistance; ↓afterload.

B. ↑ O_2 supply: ↑ coronary blood flow:

- VD of stenosed large epicardial coronary arteries[6].
- VD of collaterals.
- Redistribution of blood to subendocardial ischemic areas[7].

N.B.: Antiplatelet activity contributes to their antianginal effect.

---

[6] With moderate doses if atherosclerosis is not severe.

[7] Venodilatation → pooling of blood in splanchnic area & extremeties→ ↓ venous return →↓ ventricular filling → ↓ coronary artery compression in subendocardium → redistribution of blood flow to subendocardial ischemic areas.

Indications

1. All types of angina pectoris.
2. Congestive heart failure & acute pulmonary edema.
3. Acute myocardial infarction (early; ↓ infarct size).
4. Hypertensive emergencies.

Adverse Reactions

1. Throbbing headache[8]- flushing.
2. Postural hypotension, dizziness & syncope (potentiated by sildenafil).
3. Reflex tachycardia (due to ↓BP) → worsening of angina (↓by adding a βB).
4. Rapid tolerance with chronic use[9] (due to↓SH groups required for nitrosothiol formation & VC due to activation of adrenergic & renin-angiotensin systems).
5. Withdrawal angina with sudden cessation.
6. Methemoglobinemia[10] (rare)

Contraindications: severe hypotension occurs if nitrates are given→

1. With sildenafil.
2. In hypertrophic obstructive cardiomyopathy.
3. In right ventricular infarction (↓ preload→ ↓contractility → marked ↓ BP).
4. In volume depletion & severe aortic stenosis (used cautiously).

Precautions

1. Drug is placed in tightly closed containers → replenish supply / 3 months.
2. Instruct patient to sit while taking drug & to lie down if syncope occurs.
3. Remove tablet on relief so that only the minimal effective dose is used.
4. To avoid tolerance; allow a nitrate free period for 8 hrs/day.
5. Nitrates should not be abruptly stopped to avoid precipitation of angina.

---

[8] Due to vasodilation of meningeal arteries.Treated by aspirin.

[9] Chronic use may result in endothelial dysfunction.

[10] With chronic high doses (more with nitrites) → oxidize Hb into metHb treated by methylene blue.

Preparations & kinetics[11]

1. **Nitroglycerin & isosorbide dinitrate** (ISDN)[12] → extensive 1st pass
    a. **Sublingual tablets & spray**: rapid onset/ short-action: 2 min /30 min for nitroglycerin & 5 min /1 hr for ISDN→1st choice for acute attack[13] & for immediate prophylaxis (if exertion is expected).
    b. **Transdermal patch**: (delayed onset /longest duration → for long term prophylaxis & CHF (applied for 14 hrs/d).
    c. **IV infusion** →for AHF or unstable angina.
    d. **Oral slow-release preparation**: (alternative to transdermal).

2. **Isosorbide mononitrate**
    - No 1st pass hepatic metabolism →higher bioavailability.
    - Slower onset; longer action: given twice / day or oral extended release preparation once or twice/ day.

B. β - Blockers

(Bisoprolol- Metoprolol)

Mechanism of antianginal effect

A. **↓ O_2 demand**:
- ↓ HR & contractility.
- ↓ BP.
- Inhibit lipolysis →↓FA utilization.

Long term prophylaxis

- ↓Frequency & severity of attacks.
- Control HR at rest (50- 60 /min).
- Blunt the ↑ in HR & BP during exercise.

B. **↑ O_2 supply**:
- ↑ coronary filling in diastole (↓ HR → ↑ diastolic period).
- Redistribution of coronary flow to subendocardial ischemic areas.

N.B.: Antiplatelet activity contributes to their antianginal effect.

All βBs are equally effective except those with ISA → may ↑ HR.

---

[11] Also available as nitroglycerin ointment & chewable (ISDN) → longer action →300 min.
[12] Converted in liver into 2 molecules of mononitrate.
[13] Maximum of 3 tablets in 15 mins (5 mins apart). If pain not relieved, patient is referred to hospital.

C. Calcium Channel Blockers (CCBs)

Mechanism of action:

- CCBs act on α_1 subunit of L-type Ca^{++} channel in conductive tissues (SAN & AVN), cardiac myocytes & vascular smooth muscle including coronaries.

<table>
<tr><th colspan="2">Classification of CCBs</th></tr>
<tr><td>I. Dihydropyridine (DHP)
A. Short-acting: nifedipine
B. Intermediate acting
• Nicardipine - nimodipine
C. Long-acting
• Amlodipine - fenoldipine
• Extended release nifedipine</td><td>II. Non-Dihydropyridine (Non-DHP)
• Verapamil
• Diltiazem
(have short half lives but extended release preparations for single daily dose are available).</td></tr>
<tr><th colspan="2">Pharmacological Actions of CCBs
I. Cardiovascular Actions</th></tr>
<tr><td>Vaso-selective
Vessels > Myocardium > SAN, AVN</td><td>Non selective
SAN, AVN > Myocardium = Vessels</td></tr>
<tr><td colspan="2">A. Vascular Effects
• Peripheral arteriolar vasodilatation → ↓ PR → ↓ ABP.
• More marked with dihydropyridines [14]</td></tr>
<tr><td>B. Minimal direct cardiac depression :
• No effect on SAN & AVN conduction.
• Reflex Tachycardia: (nifedipine> amlodipine).
• Mild inhibition of contractility.</td><td>B. Direct cardiac depression:
• ↓ SAN & AVN conduction
• Bradycardia.
• Suppress contractility.</td></tr>
</table>

N.B.: Verapamil is more cardio-depressant than diltiazem.

---

[14] Nimodipine is selective on cerebral vessels.

II. Other Actions of CCBs	
• Relaxation of GIT, bronchial, urinary, uterine smooth muscles... etc. • Inhibit platelet agreggation.	
Adverse Effects of CCBs	
I. DHP	**II. Non-DHP**
1. Reflex tachycardia → worsen angina. 2. Hypotension - headache, flushing. 3. Ankle edema[16] - dizziness - tinnitus.	1. Bradycardia & heart block[15]. 2. Hypotension - heart failure. 3. Constipation (verapamil).

Therapeutic Uses

1. Angina (all types; of choice in vasospastic): diltiazem & long acting DHPs preferred:
   A. ↓ O_2 demand: due to
   - Negative chronotropic & inotropic effects (more with verapamil & diltiazem).
   - ↓ Peripheral resistance (especially with DHPs)

   B. ↑ coronary blood flow: due to dilatation of epicardial coronary arteries.
2. Hypertension: DHPs - verapamil - diltiazem (long acting DHPs induce smooth hypotension with less reflex tachycardia → preferred to short acting DHPs).
3. Supra ventricular arrhythmia: (verapamil); see arrhythmia
   - PSVT: (block AVN reentry).
   - Control heart rate in atrial fibrillation & flutter.
4. Hypertrophic obstructive cardiomyopathy (HOCM)[17]
   - **Verapamil** (of choice):
     Relieves outflow tract obstruction through its relaxant action →↓ ventricular septal thickening.

After Verapamil **Before Verapamil**

5. Other uses:
   - Peripheral vascular diseases - migraine prophylaxis – prevent premature labour.

---

[15] Paradoxical cardiac acceleration in patients with AF + WPW.
[16] Ankle edema is due to dilation of arterioles more than venules.
[17] Thickening of interventricular septum which results in obstruction of flow through left ventricular outflow tract. Aggravated by agents that ↑myocardial contractility & relieved by -ve inotropes.

Other antianginal agents

Trimetazidine:

- Metabolic drug that switches myocardial metabolism from FFA oxidation (needs more O_2) to glucose metabolism (needs less O_2) →↓ O_2 demand.
- Given in combination with other antianginal drugs.

Precautions

1. Reduce dose by 50% in renal impairment.
2. Contraindicated in parkinsonism.

Ivabradine:

- Selectively inhibits the pacemaker I_f current →↓cardiac pacemaker activity, slowing the heart rate and allowing more time for blood to flow to the myocardium.

Indications

1. Ischemic heart disease.
2. Systolic heart failure.

Precautions

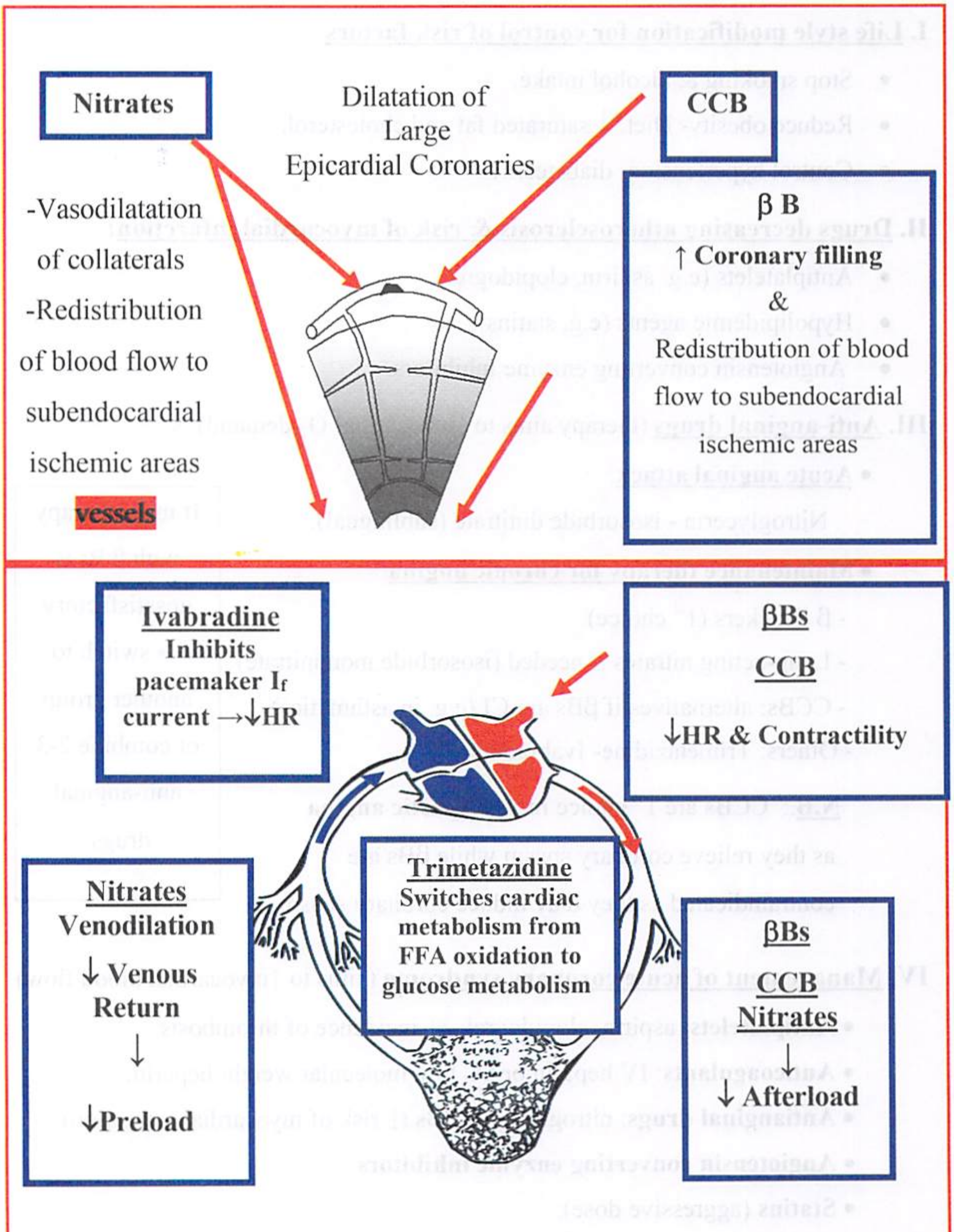
1. Contraindicated with CCBs (inhibits metabolism of CCBs).
2. Used cautiously with βBs.

Ranolazine:

- Inhibits late phase of Na current (late I_{Na}) →↓ Na^+ & Ca^{++} overload, improving diastolic function & improving oxygen supply & demand balance.
- Used in chronic angina (alone or in combination), if other drugs fail.

Side effects:

1. Prolongs QT interval.
2. Drug interactions (extensively metabolized in liver by CYP3A4).



Nitrates

Dilatation of Large Epicardial Coronaries

CCB

-Vasodilatation of collaterals
-Redistribution of blood flow to subendocardial ischemic areas

vessels

βB
↑ Coronary filling
&
Redistribution of blood flow to subendocardial ischemic areas

Ivabradine
Inhibits pacemaker I_f current →↓HR

βBs
CCB
↓HR & Contractility

Nitrates
Venodilation
↓ Venous Return
↓
↓Preload

Trimetazidine
Switches cardiac metabolism from FFA oxidation to glucose metabolism

βBs
CCB
Nitrates
↓
↓ Afterload

Summary of Effects of Anti-anginal Drugs on O_2 Supply & Demand

Management of Ischemic Heart Disease

I. Life style modification for control of risk factors

- Stop smoking & alcohol intake.
- Reduce obesity- Diet: ↓ saturated fat and cholesterol.
- Control hypertension, diabetes,...

II. Drugs decreasing atherosclerosis & risk of myocardial infarction:

- Antiplatelets (e.g. aspirin, clopidogrel).
- Hypolipidemic agents (e.g. statins).
- Angiotensin converting enzyme inhibitors.

III. Anti-anginal drugs (therapy aims to ↓myocardial O_2 demand)

- **Acute anginal attack**:

  Nitroglycerin - isosorbide dinitrate (sublingual).

- **Maintenance therapy for chronic angina**

  - β Blockers (1st choice).
  - Long-acting nitrates if needed (isosorbide mononitrate)
  - CCBs: alternatives if βBs are CI (e.g. in asthmatics).
  - Others: Trimetazidine- Ivabradine

  N.B.: CCBs are 1st choice **in vasospastic angina** as they relieve coronary spasm while βBs are contraindicated as they may induce coronary spasm.

If monotherapy with β Bs is unsatisfactory → switch to another group or combine 2-3 anti-anginal drugs.

IV. Management of acute coronary syndrome (aims to ↑myocardial blood flow)

- **Antiplatelets**: aspirin, clopidogrel→↓ incidence of thrombosis.
- **Anticoagulants**: IV heparin or SC low-molecular weight heparin.
- **Antianginal drugs**: nitroglycerin- βBs (↓ risk of myocardial infarction).
- **Angiotensin converting enzyme inhibitors.**
- **Statins** (aggressive dose).
- **Fibrinolytics**; within first 6 hours of myocardial infarction.

V. Revascularization & angioplasty (except in vasospastic angina).

DRUG THERAPY OF HEART FAILURE

Definition of systolic heart failure

- Systolic heart failure (HF) is a condition in which the heart is unable to pump an adequate supply of blood for the metabolic needs of the body at normal ventricular filling pressures provided that there is an adequate venous return.

Types of Heart failure:

- Depending on the time course of HF: Acute (AHF) & chronic (CHF) heart failure.
- Depending on the level of COP: Low and high[18] COP failure.

Clinical features of low COP failure

- If preload is markedly ↑ → patient complains mainly from **congestive manifestations** e.g. leg edema, congested tender liver (for Rt side HF) or cough, hemoptysis, dyspnea up to pulmonary edema (for Lt side HF).
- If afterload is markedly ↑ → patient complains mainly from **low cardiac output manifestations** e.g. dyspnea 2^{ry} to pulmonary oligemia (in Rt side HF) or dizziness, fatigue, cold hands, oliguria, cyanosis, syncope (in Lt side HF).

Pathophysiology of Heart Failure

- The heart receives blood returning from body organs (preload) in diastole to eject it against peripheral resistance (afterload) in systole. HF results from severely impaired contractility or marked ↑ in one or both cardiac loads[19].
- Systolic ventricular dysfunction is characterized by:
  i. ↓Stroke volume (SV) & a concomitant increase in end diastolic volume (EDV) → ↓ ejection fraction (SV/ EDV).
  ii. ↑End diastolic pressure (EDP) in left ventricle→ ↑pulmonary venous & capillary pressure → pulmonary congestion, dyspnea & pulmonary edema.
- Before this stage of HF, the body develops compensatory mechanisms to maintain cardiac output. However these mechanisms eventually fail.

---

[18] In anemia, thyrotoxicosis, or A-V fistula with no cardiac abnormality; treat underlying causes.
[19] Due to a 1^{ry} insult to the myocardium e.g., infarction, ↑ hemodynamic load or inflammation.

Neurohumoral compensatory mechanisms in HF

- Inability of the heart to maintain a normal BP & organ perfusion → reflex stimulation of baroreceptors→ activation of the adrenergic & renin-angiotensin systems → peripheral VC, ↑aldosterone with salt & water retention, ↑ heart rate & left ventricular hypertrophy →**compensated HF**.
- Persistent activation of the adrenergic & renin-angiotensin systems → marked ↑ in preload & afterload on the already impaired cardiac muscle → ventricular dilation & ↑ O_2 consumption with fixed O_2 supply → damage of cardiac myocytes→ more ↑ EDV & EDP with more ↓COP → **decompensated HF**

Management of Heart Failure

		I. **↓ Preload** **Improve congestion**	**II.** **↓ Afterload** **Improve low COP**	**III.** **↑Contractility** **Improve low COP & congestion**	**IV.** **Protect Heart** **&/or restore its function**
Lines of Treatment		• Salt & Fluid restriction. • Diuretics. • Venodilators	• Physical/ mental rest. • Arteriodilators	• Positive inotropics.	• β-blockers • Aldosterone antagonists
Drugs Used	**For CHF**	• Loop diuretics • ACEIs. • ARBs. • Nitrates	• ACEIs • ARBs. • Hydralazine	• Digoxin	• β-blockers Carvedilol Bisoprolol Metoprolol • Spironolactone • Eplerenone
	For AHF	• Loop diuretics • Nitrates. • Nitroprusside	• Nitroprusside	• Dopamine. • Dobutamine. • Inamrinone.	

N.B.: - ACEIs, ARBs & nitroprusside are mixed arteriovenodilators.
- Mortality rate in HF (30% per year) is ↓ by ACEIs, ARBs, βBs & spironolactone.

Other Agents used in heart failure

1. Sacubitril-valsartan

- Combination of the ARB "valsartan" & "sacubitril" an inhibitor of neprilysin enzyme that degrades atrial natriuretic peptide "ANP →↑ ANP → Na excretion, diuresis, vasodilation. ANP also inhibits RAS.
- Used instead of ACEI or ARB in patients with class II - IV heart failure with LVEF ≤40 %, with persistent symptoms despite optimal combination therapy. Some clinicians use it from the start to↓ Mortality & morbidity.

2. Tolvaptam

- ADH antagonist (vasopressin, V2 receptor antagonist). Used in systolic heart failure → excretion of electrolyte-free water → corrects dilutional hyponatremia, secondary to increase ADH in heart failure[1].

N.B.: **N-3 polyunsaturated fatty acids** can reduce mortality in CHF.

Order of therapy in CHF

1. **Loop diuretics** are introduced 1st for patients with congestive manifestations.
2. **ACEIs** →during or after stabilization on diuretics. If not tolerated give **ARBs**.
3. **Beta blockers** (start with low dose) → in patient stable on ACEIs or ARBs.
4. **Mineralocorticoid receptor antagonists (MRAs):**[2] If still symptomatic.
5. **Sacubitril-valsartan: instead of ACEIs or ARB**, if still symptomatic.
6. **Ivabradine: added If HR ≥ 70.**
7. **Reduce dose of diuretic**: If symptoms improved.
8. **Digoxin or hydralazine + isosorbide dinitrate** (fixed dose tablet): If not improved.

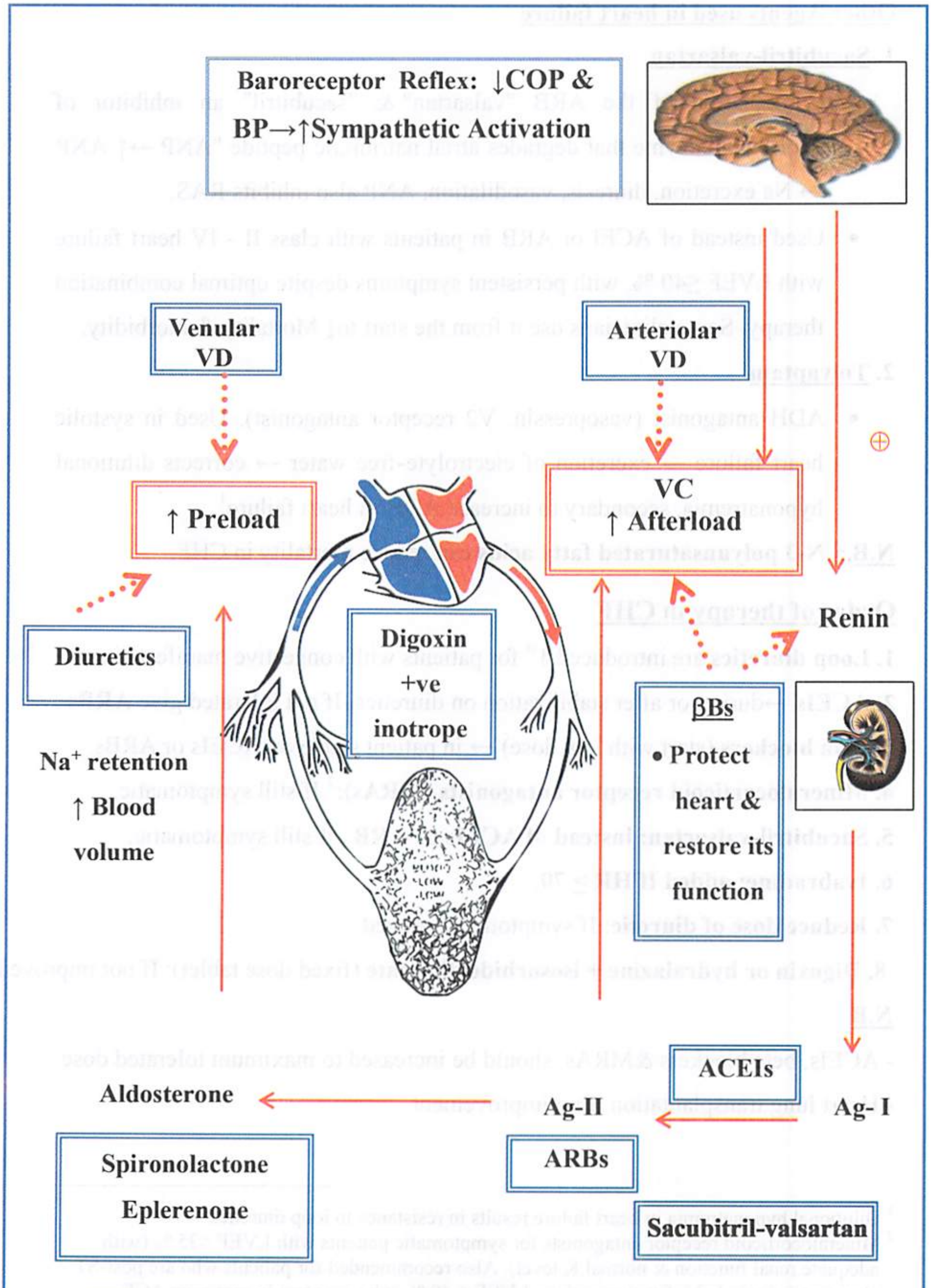
N.B.:

- ACEIs, beta blockers &MRAs should be increased to maximum tolerated dose.
- Heart lung transplantation if no improvement.

---

[1] Dilutional hyponatremia in heart failure results in resistance to loop diuretics

[2] Mineralocorticoid receptor antagonists for symptomatic patients with LVEF <35 % (with adequate renal function & normal K level). Also recommended for patients who are post-ST elevation myocardial infarction with an LVEF ≤ 40 %, who are already receiving ACE inhibitor, and have either symptomatic HF or diabetes. Therapy is limited to patients with baseline serum potassium <5.0 mEq/L & glomerular filtration rate >50 mL/min per 1.73 m^2


Baroreceptor Reflex: ↓COP & BP→↑Sympathetic Activation
Venular VD
Arteriolar VD
⊕
↑ Preload
VC ↑ Afterload
Renin
Diuretics
Digoxin +ve inotrope
βBs
• Protect heart & restore its function
Na⁺ retention
↑ Blood volume
ACEIs
Aldosterone
Ag-II
Ag-I
Spironolactone
Eplerenone
ARBs
Sacubitril-valsartan

Pathophysiology & Drug Therapy of Heart Failure

Individual Drugs Used in Heart Failure

I. VASODILATORS

VENODILATORS

Nitrates

- ↓ Venous return &↓ preload → ↓systemic or pulmonary congestion → improves congestive symptoms.

ARTERIODILATORS

Hydralazine

- ↓ Peripheral resistance & ↓ afterload →↑COP → improves symptoms of low COP.

MIXED DILATORS

1. **Sodium nitroprusside**
    - In Acute HF.
2. **ACEIs**
    - Best in CHF.
3. **ARBs**
    - If ACEIs are not tolerated.

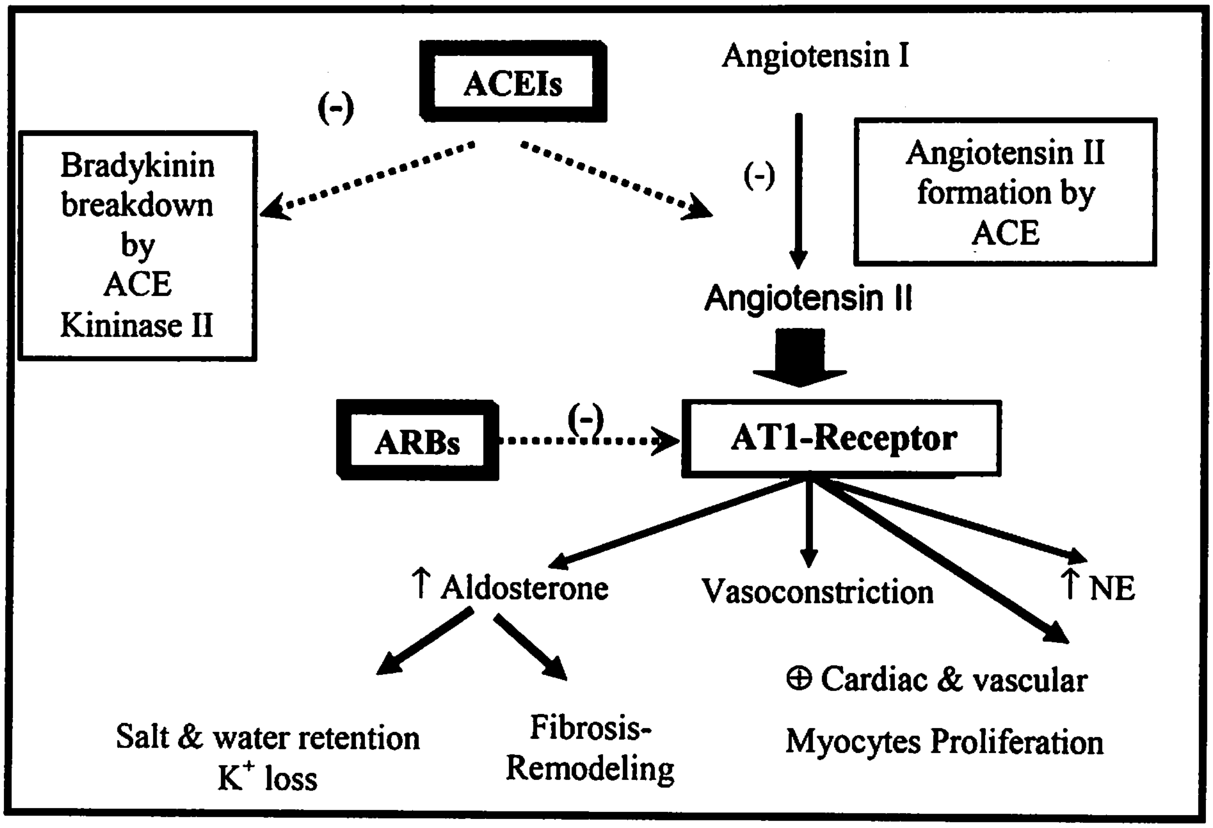
A. Angiotensin-Converting Enzyme Inhibitors (ACEIs)

Mechanism of Action

- They inhibit the angiotensin converting enzyme, responsible for Angiotensin II formation & bradykinin breakdown, resulting in:
  - ↓ Angiotensin II.
  - ↑ Bradykinin →↑vasodilator PG & NO.

These effects lead to:

1. Vasodilatation of both arteries (↑ COP) & veins (↓ venous congestion).
2. Inhibition of aldosterone secretion → Na^+ & water loss with K^+ retention.
3. Prevention of myocardial hypertrophy & remodeling following myocardial infarction (with ACEIs that inhibit tissue ACE; e.g. fosinopril).
4. Block central & peripheral NE release induced by angiotensin II → ↓ BP without reflex tachycardia (blunt sympathetic reflexes).


ACEIs
(-)
Angiotensin I
Bradykinin breakdown by ACE Kininase II
(-)
Angiotensin II formation by ACE
Angiotensin II
ARBs
(-)
AT1-Receptor
↑ Aldosterone
Vasoconstriction
↑ NE
⊕ Cardiac & vascular Myocytes Proliferation
Salt & water retention K⁺ loss
Fibrosis-Remodeling

Formation & effects of Ag II & Sites of action of ACEIs & ARBs

Advantages of ACEIs

- Improve exercise tolerance & congestive symptoms (↓preload & afterload) &↓ cardiovascular mortality in HF[24].
- Renoprotective especially in diabetics.
- Do not induce reflex tachycardia, salt & water retention ....etc

Indications:

1. **Hypertension**: see indications of ACEIs in hypertension.
2. **Heart failure**: all cases of LV dysfunction (early cases →end stage HF).
3. **Acute myocardial infarction**

   Used early in MI (in the first 24 hrs plus aspirin, fibrinolytics & βBs)[25]:

   a. Inhibit aldosterone-induced remodeling & prevent heart failure

   b. ↓ sudden death (prevent arrhythmia 2^{ry} to hypokalemia & sympathetic overactivity).
4. **Nephropathy**: diabetic or nondiabetic.

Members of ACEIs:

- **Captopril**: 1st ACEI, short acting ($t_{½}$ < 2 h) → taken 3 times/day (not a prodrug).
- **Enalapril – Perindopril - Ramipril - Lisinopril - Fosinopril**
  - All (except lisinopril) are prodrugs requiring activation in liver.
  - Long duration (given once/day)[26].
  - Lisinopril may be given in liver disease (no hepatic metabolism).
  - Fosinopril is highly lipid soluble with dual elimination; hepatic & renal→ no need for dose adjustment in renal disease. It may have a greater effect on tissue ACE in the heart.
  - Enalaprilat: active metabolite of enalapril. The only ACEI given IV→ used in emergency.

---

[24] Captopril was the first single drug observed to ↓ cardiovascular mortality.

[25] ↓ Mortality when given in pre-infarction period.

[26] Long duration of action is due to long acting metabolites.

Side Effects of ACEIs

MOST COMMON

Chronic dry cough

- Late.
- (30% of patients).
- Due to bradykinin accumulation.

LESS COMMON

- **1st dose hypotension** → start with low dose at evening.
- **Hyperkalemia**:
  - Especially if given with K^+- sparing diuretics, βBs or in renal impairment.
- **Hypersensitivity:**
  - Rash & pruritis.
- **GIT:**
  - Anorexia- vomiting.
  - Taste disturbance.
  - Diarrhea.

MOST SERIOUS

Angioedema

- Early (but may occur later).
- Rare but fatal.
- Due to bradykinin accumulation?

SERIOUS

- **Renal impairment** (reversible):

  More common in high renin states:

  a. Patients on diuretics→↓ diuretic dose or stop it 24 h before ACEIs.

  b. Bilateral renal artery stenosis →**CI** (since GFR is maintained by VC of efferent arteriole by AgII).
- **Bone marrow depression.**
- **Fetotoxic:** if given in last trimester.
- **Teratogenic** if given in 1st trimester.

B. Angiotensin II Receptor Blockers
(ARBs)

Members:

- Old: Valsartan - Losartan.[27]
- New: Candesartan – Irbesartan - Eprosartan -Telmisartan.

Mechanism of action:

- Block AT_1 receptor which mediates most of the pathological cardiovascular effects of Ag II.
- Spare AT_2 receptor → vasodilation & anti-proliferative effects.

Side effects (well tolerated):

1. Hyperkalemia.
2. Taste disturbance.
3. Angioedema.
4. Unsafe on fetus.
5. Acute renal failure (in renovascular hypertension or in hypovolemia).

Disadvantages compared to ACEIs

- Lack of vasodilator effects of BK.

Advantages over ACEIs

- No BK production→ no cough (angioedema still occurs).
- Antagonize Ag II formed by ACE & non-ACE pathways[28].
- Avoid hormonal "escape" (↑ renin) seen with prolonged ACEIs therapy.
- ↑Activity of AgII at AT2 receptor →↑VD & antiproliferative effects.

- ARBs are alternatives to ACEIs if the latter are not tolerated.

---

[27] Losartan is preferred in hypertension with stroke.

[28] In heart, kidney & blood vessels, Ag II may be formed by enzymes other than ACE, e.g., chymase.

C. Hydralazine

Mechanism of Action

- Arteriolar vasodilator: K^+ channel opener → hyperpolarization → inhibition of Ca^{2+} influx into vessel wall.

Disadvantage: chronic use → rapid tolerance due to reflex activation of sympathetic & renin-angiotensin systems → salt retention & ↑ HR.

Indications

- **Heart failure**: given with nitrates, but ACEIs largely replaced it (as it induces lupus syndrome in slow acetylators).
- **Hypertension**: IV in eclampsia.

D. Sodium Nitroprusside

Mechanism of Action

- Nitric oxide donor →↑ c- GMP which induces vasodilation by inhibiting Ca^{2+} influx into the wall of blood vessels.

Indications: very potent & rapidly acting, thus used in→

1. Most hypertensive emergencies e.g. hypertensive encephalopathy.
2. Severe acute heart failure, especially with severe rise of BP.

Toxicity

1. Severe hypotension and myocardial ischemia (due to reflex tachycardia).
2. Cyanide[29] & thiocyanate toxicity: CNS side effects & delayed hypothyroidism

Precautions

- Given by slow IV infusion (immediate onset with $t_{1/2}$ 2 min).
- Solution is freshly prepared in saline,covered with opaque foil (sensitive to light).
- Frequent monitoring of BP (avoid drop of BP below 95 / 70 mmHg).
- Avoid prolonged administration to ↓ cyanide & thiocyanate toxicity.

---

[29] Nitroprusside metabolism releases free cyanide ion → converted to thiocynate & excreted in urine. Cyanide toxicity is treated by sodium nitrite, sodium thiosulphate, hydroxycobalamin & methylene blue.

II. Diuretics

Mechanism of Action

- Diuretics are given for fluid control in cases with symptomatic HF & fluid retention → ↓plasma volume → ↓venous return & preload → ↓pulmonary congestion (↓orthopnea & nocturnal dyspnea) - ↓ peripheral (ankle) edema.

Preparations

- **Loop Diuretics**: 1st choice especially in refractory or pulmonary edema (IVI).
- **Thiazides**: may be added in refractoriness to loop diuretics.
- **Spironolactone**: added[30] to loop diuretics & ACEIs→↓ mortality by 30%, by antagonizing systemic & local effects of excess aldosterone resulting in:
  a. ↓ Na^+ retention and worsening of edema.
  b. Minimize diuretic- induced hypokalemia →↓ arrhythmia & sudden death.
  c. ↓ Myocardial hypertrophy & fibrosis induced by local aldosterone.

III. Beta Blockers

- Carvedilol, bisoprolol & metoprolol decrease mortality by 30% when added to ACEIs & diuretics in hemodynamically stable patients[31].
- Block the **Sympathetic and Renin angiotensin system** activation in HF.

Beneficial effects in HF

1. ↓ HR → ↑ coronary flow.
2. ↓ Afterload and ↓ O_2 demand.
3. Cardioprotection: block catecholamine & Ag II - induced arrhythmia, myocardial damage & apoptosis.
4. Improve LV remodeling.
5. Resensitize the downregulated β_1 receptors (in long standing HF) → improve cardiac contractility.

---

[30] Cautiously, to avoid hyperkalemia especially if ACEIs are used or in patients with renal impairment.

[31] Transient worsening in cardiac function may occur → start with low dose & gradually titrate to more tolerable doses.

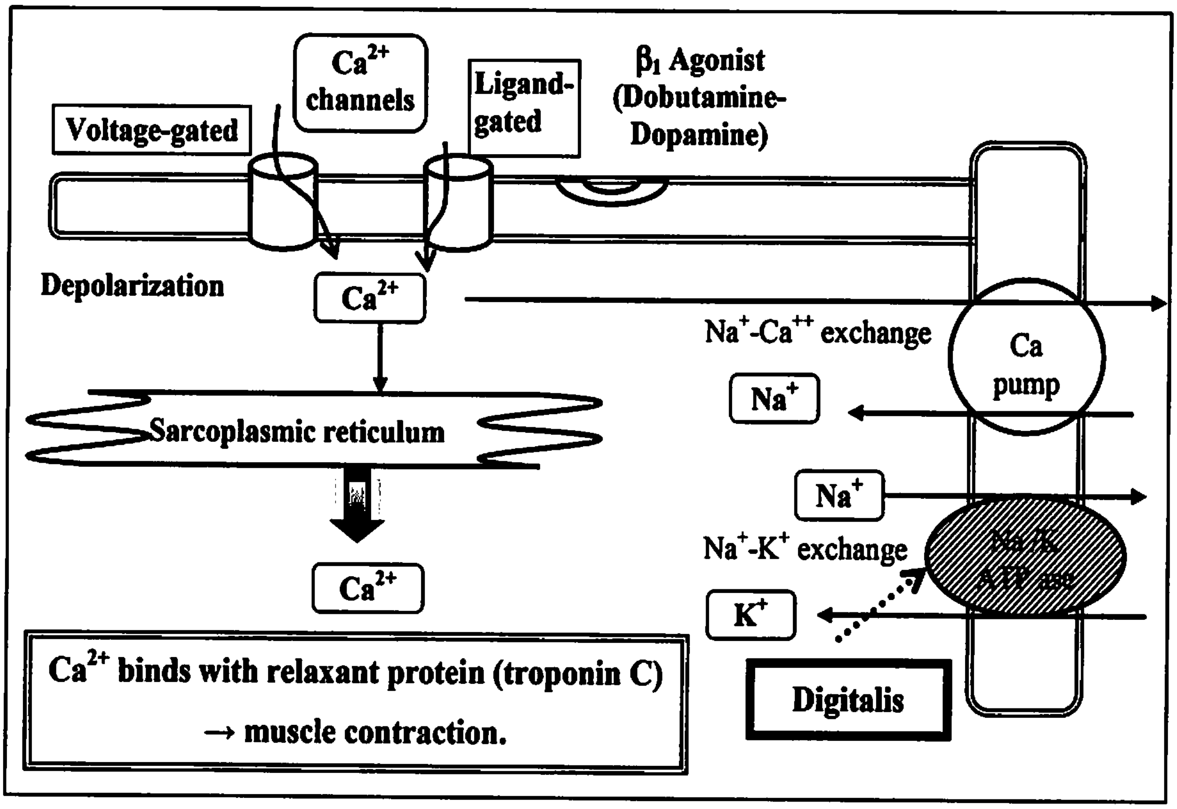
IV. Positive Inotropic Drugs

1. Cardiac Glycosides

Digitalis (Digoxin)

Mechanism of Myocardial Contraction

- Myocardial contraction occurs after influx of Ca^{2+} through specific channels:
  1. Voltage-gated Ca^{2+} channel which is activated by membrane depolarization.
  2. Ligand-gated Ca^{2+}channel which is activated by β_1-receptor stimulation.
- Ca^{2+} influx → ↑ intracellular Ca^{2+} → Ca^{2+} release from SR → ↑ cytosolic Ca^{2+} → ↑ myocardial contraction by binding with relaxant protein troponin C.
- Cardiac relaxation occurs after cytosolic Ca^{2+} is reduced by reuptake of Ca^{2+} into the sarcoplasmic reticulum & Ca^{2+} exit in exchange with Na^+ via the Na^+ - Ca^{2+} exchange (Ca pump).
- Na^+ is then pumped out in exchange with K^+ by $^{Na+}/K^+$ ATPase.


Ca²⁺ channels
Voltage-gated
Ligand-gated
β₁ Agonist (Dobutamine-Dopamine)
Depolarization
Ca²⁺
Na⁺-Ca⁺⁺ exchange
Ca pump
Na⁺
Sarcoplasmic reticulum
Na⁺
Na⁺-K⁺ exchange
Na-K ATPase
Ca²⁺
K⁺
Ca²⁺ binds with relaxant protein (troponin C) → muscle contraction.
Digitalis

Molecular mechanism of action of digitalis (Na^+ pump inhibition)

- Digitalis inhibits membrane-bound Na^+/K^+ activated ATPase responsible for Na^+ outflux in exchange with K^+ influx → ↑ intracellular Na^+.
- ↑ Intracellular Na^+ → inhibits outflux of cytosolic Ca^{2+} in exchange with Na^+ influx → ↑ cytosolic Ca^{2+}.
- ↑ intracellular Na^+ & cytosolic Ca^{2+}→ ↑ activity of excitable tissues in cardiac & smooth muscle & neurons (CNS) leading to the following effects:

1. Positive Inotropic Effect

- ↑ Cytosolic Ca^{2+} in myocardium → inhibits troponin C (relaxant protein) → ↑ myocardial contractility → ↑ COP in HF → maintains organ perfusion & BP & ↓ baroreflex stimulation of adrenergic & renin- angiotensin systems.

Consequences of positive inotropic effect

a. ↓ Venous Pressure:

- Due to ↑ COP with better cardiac emptying & subsequent filling; ↓ overstretching of the heart.

b. ↓ Baroreflex sympathetic over-activity:

- ↓ Peripheral resistance & cardiac loads.
- ↓ Cardiac over-stimulation (↓ HR).
- ↓ Renin (↓ Na^+ retention & edema).

c. Diuresis:

- Due to ↑ COP →↑renal blood flow & GFR (plus a direct anti-aldosterone action → inhibition of Na^+/K^+ exchange in distal tubules).

2. Electrical effects:

- ↑Intracellular Na^+ & Ca^{++} → shifts membrane potential towards firing threshold at the end of action potential (AP) → delayed after-depolarization (DAD) → ventricular premature beats, tachycardia or fibrillation.
- Activates K^+ channels → rapidly ends AP → ↓ atrial APD & ERP → converts atrial flutter to atrial fibrillation (AF) & paroxysmal AF to permanent AF.

3. Autonomic effects

A. Vagal stimulation (at therapeutic dose)[32]

- Inhibits SAN →↓ HR (indicator for optimal digitalization).
- AVN block & ↑ ERP→
  - Bradycardia, heart block (treated by atropine).
  - Protects ventricle from rapid atrial rate in atrial flutter and AF.
  - Terminates attack of PSVT by interrupting AVN re-entry.

B. Sympathetic stimulation (at toxic dose) →arrythmogenic potential.

4. CNS stimulation

- Vagal center stimulation (therapeutic doses).
- Vomiting; CTZ stimulation[33] (supratherapeutic doses)
- Visual & cortical stimulation→visual disturbances, hallucinations (toxic dose).

5. Direct Vasoconstriction: ↑ Ca^{2+} in vessel wall (offset by ↓ sympathetic activity).

Pharmacokinetics

Variable between patients & in same patient with different preparations. Roughly:

- ⅔ of oral dose is rapidly absorbed; rest is inactivated by intestinal flora.
- ⅔ of drug is unbound to plasma proteins (wide tissue distribution → CNS).
- ⅔ is excreted unchanged renally & rest by stool & hepatically → **$t_{½}$ 36 hrs.**
- Narrow safety margin: therapeutic level (0.5-1.5) close to toxic (>2 ng/ml).

Dosing of digoxin (Digitalization):

- To achieve therapeutic blood levels & to avoid toxicity: low dose 0.125-0.25 mg/d (Css is reached in one week).

---

[32] Due to central vagal stimulation, baroreceptors sensitization, ↑ muscarinic transmission.

[33] It also induces local GIT irritation.

Drug Interactions with Digoxin

I. Pharmacokinetic Interactions[34]

1. Erythromycin →↓ inactivation of digitalis by killing GIT flora→↑absorption.
2. Antiarrhythmics (quinidine, amiodarone & verapamil) →↓ renal excretion of digoxin & displace it from tissue binding sites & from plasma proteins.

II. Pharmacodynamic Interactions

1. Diuretics (→ hypokalemia & hypomagnesemia[35]).
2. Hypercalcemia.
3. Sympathomimetics.

↑ Digitalis - induced Tachyarrhythmias

4. β Blockers & CCBs: inhibit SAN & AV node → **complete heart block.**

Indications for Digitalis

1. **CHF:**
   a. Symptomatic HF despite therapy with diuretics & ACEIs.
   b. HF **plus AF (most solid indication):** positive inotropic →↑ COP in HF & blocks AVN→ controls ventricular rate in AF.
2. **Chronic AF without HF:**
   a. Plus verapamil or β B to control ventricular rate.
   b. Before procainamide & quinidine to counteract their atropine-like action.
3. **Paroxysmal supraventricular tachycardia:** vagal effect on AVN ends attack.

Contraindications

1. Acute MI & rheumatic carditis (irritable myocardium → arrhythmia).
2. HOCM: inotropic →↑ outflow tract obstruction.
3. Sick sinus syndrome → converted to cardiac arrest (vagal effect).
4. AF+WPW: paradoxical↑ HR (blocks AVN →↑ conduction in accessory tract).
5. Partial/ incomplete heart block → converted to complete heart block (vagal effect).
6. Ventricular tachycardia → precipitates ventricular fibrillation.

---

[34] Metoclopramide → ↑ GIT motility →↓absorption.. Anticholinergics →↓ GIT motility →↑absorption.

[35] Digitalis competes with K^+ for its site on Na^+/K^+ ATPase. Mg^{2+} opposes Ca^{2+}.

Digitalis Toxicity (GCCG)

1. GIT Upsets: anorexia, nausea, vomiting and diarrhea (early symptoms).
2. Cardiac Arrhythmia:
   a. Supraventricular & ventricular; premature beats, tachycardia or fibrillation.
   b. Sinus bradycardia and heart block (↑ vagal tone).
3. CNS manifestations: confusion, hallucination, yellow & green colored vision.
4. Gynecomastia (steroid nucleus).

Treatment of Toxicity

1. Stop digitalis & the K losing diuretic.
2. KCl: if serum potassium is < 3.5 mmol/l; C.I. in heart block[36].
3. Lidocaine or phenytoin in V. arrhythmia (→ do not impair AV conduction)[37].
4. Atropine in bradycardia and heart block (pacing is used if no response).
5. Digibind (fab): antibodies that bind digoxin → eliminated in urine (in fatal toxicity).

2. Dopamine

- ↑ Renal blood flow (low dose→ D_1 renal vasodilation).
- ↑ COP (intermediate dose → β_1 cardiac stimulant).
- ↑ BP with VC (high dose→ α_1 vasoconstriction).

Indications

- Acute HF & cardiogenic shock e.g. after MI or surgery especially if there is renal involvement (→ renal VD) or hypotension (→↑ BP).
- Chronic refractory heart failure.

3. Dobutamine

- Positive inotrope (β_1), minimal effect on HR & BP.
- Uses are similar to DA but used in normotensives (no α-effect) with preserved renal function (no renal vasodilation).

---

[36] Other contraindication: hyperkalemia or renal impairment.

[37] Cardioversion (DC): may worsen digitalis arrhythmia thus reserved for ventricular fibrillation.

4. Phosphodiesterase III Inhibitors

Milrinone – Inamrinone

Mechanism:

- Inodilators, inhibit phosphodiesterase III→↓ cAMP breakdown:
  1. ↑ cardiac contractility → ↑COP.
  2. Vasodilation → arterial (↓ afterload & PR), venous dilators (↓preload & pulmonary congestion) → ↓ left & right cardiac filling pressures.

Indications:

- Short term treatment of HF especially, acute or chronic refractory.

Adverse Effects:

- GIT upset.
- Thrombocytopenia - arrhythmia.

Acute De-compensated Heart Failure (ADHF)

A. **Initial therapy** includes the following:

- **Supplemental O_2**: for ADHF with decreased O_2 saturation.
- **IV loop diuretic**[38]: for ADHF + pulmonary edema (except in severe hypotension or cardiogenic shock).
- **Vasodilators: e.g.** IV nitroglycerin (in non hypotensives). Nitroprusside may be used if significant afterload reduction is needed[39].
- **Morphine**: in patients with MI (**avoid** in ADHF without acute MI[40])

B. **Positive inotropes**[41] : dobutamine or milrinone.

C. **Venous thromboembolism prophylaxis**: in hospitalized patients.

---

[38] IV bolus dosing, if inadequate, give continuous infusion of loop diuretic & add a thiazide.

[39] Hypertensive emergency, acute aortic or mitral regurgitation.

[40] Limited evidence of benefit & increased need for ventilatory support.

[41] In systolic HF (e.g. documented low ejection fraction) severe ADHF, hypotension or shock. Severe cases require mechanical cardiac assistance & ultrafiltration if refractory to diuretics.

DRUG THERAPY OF SHOCK

Shock occurs when the circulation of arterial blood is inadequate to meet the tissue metabolic needs (diminished tissue perfusion).

Types

1. **Hypovolemic shock**: intravascular volume is depleted due to
   - Hemorrhagic shock (loss of blood).
   - Burns (loss of plasma).
   - Vomiting, diarrhea or excessive sweating (loss of fluids & electrolytes).
2. **Cardiogenic shock**: mostly due to acute myocardial infarction.
3. **Distributive shock**: ↓ systemic vascular resistance as in:
   - Septic shock.
   - Anaphylactic.
   - Neurogenic: during spinal anesthesia & psychic trauma.

Hemodynamic profiles of the types of shock

Physiologic variable	**Preload**	**Pump function**	**Afterload**	**Tissue perfusion**
Clinical measurement	**Pulmonary capillary wedge pressure**	**Cardiac output**	**Systemic vascular resistance**	**Mixed venous O_2 saturation**
Hypovolemic	↓	↓	↑	↓
Cardiogenic	↑	↓	↑	↓
Distributive	↓ or ↔	↑	↓	↑

N.B.: Obstructive shock: a subtype where there is obstruction of a main channel of blood flow, e.g. massive pulmonary embolism, dissecting aortic aneurysm.

Management of different types of shock

A. Hypovolemic shock:

1. **Rapid volume repletion**: delayed therapy can lead to ischemic injury & to irreversible shock and multi-organ system failure:
    - At least 1-2 liters of isotonic saline[42] to restore tissue perfusion are initially given **rapidly** & continued at rapid rate if BP remains low.
    - **Patients with non-hemorrhagic shock**: isotonic crystalloid solution rather than a hyperoncotic starch or albumin-containing solution.
    - **Patients with hemorrhagic shock**: Red blood cell transfusions.

      N.B.: efficacy of IV bicarbonate in patients with marked hypoperfusion who develop lactic acidosis is uncertain.

B. Septic shock[43]

1. **Secure airway and correct hypoxemia.**
2. **Restoration of tissue perfusion**
    - Intravascular volume repletion: boluses of IV fluids: crystalloid solution rather than a hyperoncotic starch solution or albumin.
    - Vasopressors: if patient remains hypotensive: norepinephrine is preferred.
    - Inotropic therapy or blood transfusions: For patients whose $ScvO_2$ remains <70 % after intravenous fluid and vasopressor therapy.
3. **Identification and treatment of the site of infection**
    - Antibiotics after appropriate cultures.
    - Empiric broad spectrum antibiotics if source of infection is unidentified.
    - Abscesses should be drained & extensive soft tissue infections excised.
4. **Glucocorticoids.**
5. **Nutritional support and glucose control.**

---

[42] For large volume lactated-Ringers solution or 0.45% saline solution with 75 mmol/L of sodium bicarbonate may be used instead of isotonic saline to avoid hyperchloremic metabolic acidosis.

[43] Syndrome of systemic inflammation & widespread tissue injury due to infection. Ranges from mild sepsis to septic shock. Termed systemic inflammatory response syndrome in absence of infection.

C. Cardiogenic shock: (mostly 2^{ry} to MI, 50% mortality)

1. **Ventilation support** to correct hypoxemia and, in part, acidosis
2. **Early Aspirin + heparin**
3. **Sympathomimetic inotropes** (e.g. DA, dobutamine (in normotensives).
4. **Norepinephrine** (for refractory hypotension).
5. **Reperfusion** should be attempted in all patients:
    - **Revascularization** is the best for all patients (PCI or CABAG).
    - **Fibrinolytics** for ST elevated MI if revascularization is not feasible.
6. **Antiplatelets**: in addition to early aspirin, a thienopyridine e.g. clopidogrel & a GP IIb/IIIa e.g. eptafibatide may be added for high risk patients.
7. **Withhold beta blockers & calcium channel blockers.**

D. Anaphylactic shock[44]:

1. **Epinephrine**: (1st & most important) **IM**[45] or IV if not responding.
2. **Airway:** intubation if signs of impending obstruction from angioedema.
3. **Place patient in recumbent position**, and elevate lower extremities.
4. **Oxygen:** via facemask, or up to 100 percent oxygen as needed.
5. **Normal saline:** for hypotension, rapid IV infusion of 1 to 2 litres[46].

Additional Drugs

- **Salbutamol:** For bronchospasm resistant to IM epinephrine.
- **H_1 antihistamine:** IV diphenhydramine for relief of urticaria & itching.
- **H_2 antihistamine:** IV ranitidine.
- **Glucocorticoid:** Consider giving methylprednisolone 125 mg IV.

Treatment of refractory symptoms:

- **Epinephrine IVI[47]: if inadequate response to IM epinephrine & IV saline.**
- **Vasopressors[48]:** in addition to epinephrine.
- **Glucagon IV:** Patients on beta-blockers may not respond to epinephrine.

---

[44] Anaphylaxis: serious allergic reaction, rapid onset & fatal cardiorespiratory arrest.

[45] Epinephrine (1 mg/mL preparation): Give 0.3 to 0.5 mg IM, can repeat every 5 to 15 min.

[46] Repeat as needed; massive fluid shifts with severe loss of intravascular volume can occur.

[47] Epinephrine 2 to 10 μg/ minute by infusion pump titrated according to BP, HR & O_2.

[48] Vaspressors are given by infusion pump titrated according to BP, HR &O_2.

HYPERTENSION

Definition:

- Hypertension is an abnormal sustained rise in arterial blood pressure "ABP" (optimal level: < 120/80 mmHg).
- **Stages** (according to systolic BP/ diastolic BP)[49]:
  - **Stage 1** (mild): 140/90 → 160/100
  - **Stage 2** (moderate): 160/100 → 180/110
  - **Stage 3** (severe): >180/110

Hypertensive encephalopathy: acute severe rise of ABP that may result in serious complications e.g. cerebral haemorrhage → **emergency**, requiring aggressive therapy.

Aetiology:

- **Essential hypertension**: is due to unknown cause[50] → drug therapy is **not curative but is life long.**
- **Secondary hypertension**: is due to known causes e.g. renal, endocrinal, drugs… etc → treatment of the cause **can be curative**.

Drug-induced hypertension

1. Oestrogen/ Contraceptives.
2. NSAIDs.
3. Sympathomimetics (e.g., in OTC cold medicine).
4. Glucocorticoids.
5. Liquorice & its derivatives.

Why treat hypertension?

- Hypertension is a **silent killer** as it induces vascular damage → affects heart, brain & kidneys (→**target organ damage,** heart failure, ischemic heart disease, stroke & renal failure) & retinal artery → **blindness.**
- Treatment is not symptomatic but hypertension should be always treated even if it is silent to prevent or reverse target organ damage.

---

[49] Isolated systolic hypertension: If SBP is > 140 mmHg while the DBP is <90.

[50] However, there is exaggerated vascular muscle tone that can in part explain the ↑ in the ABP.

Treatment Strategy

I. Evaluation: The patient should be evaluated for presence of:

- Correctable aetiology (e.g. if hypertension is drug- induced → stop drug).
- Major risk factors that can ↑ TOD e.g. smoking, hyperlipidaemia, diabetes.
- TOD: e.g. hypertensive kidney diseases or clinical cardiovascular disease (CCD) e.g., ischemic heart diseases.

II. Life style modification

- Stop smoking.
- Regular exercise.
- Weight reduction.
- Restrict salt - ↑ K^+.
- ↓ Saturated fat & cholesterol.

- Life style modification alone is enough in mild cases with no TOD, diabetes or CCD but if hypertension is beyond mild stage or if there is diabetes, CCD or TOD→ initiate drug therapy.

III. Drug Therapy:

Choice of drugs[51] is based on:

1. Age, sex and race (black patients respond better to thiazides or CCBs & relatively poorly to ACEIs or βBs (low renin level).
2. Concomitant diseases e.g. diabetes, bronchial asthma, etc.
3. Concomitantly administered drugs (to avoid drug interactions).
4. Effect of drugs on quality of life.
5. Drug cost & duration of action (long acting preparations → ↑ compliance).
6. Bedtime versus morning dosing:
   - Average nocturnal BP is 15% < daytime values (dip).
   - "Non-dipping," is a stronger predictor of adverse cardiovascular outcomes than daytime BP.
   - Shifting at least one antihypertensive medication from morning to evening can restore the normal nocturnal blood pressure dip.

---

[51] Choice is not based on efficacy or degree of CV protection except in the high risk patients in which ACEIs or ARBs offer better CV protection since their cardioprotection is independent of BP lowering.

Initial Monotherapy[52]:

Classes of drugs for initial monotherapy

- Thiazide diuretics (in low dose).
- ACEIs
- Long acting CCBs.
- ARBs.

Sequential monotherapy

- Sequential monotherapy allows 60 to 80% of patients with mild hypertension to be initially controlled with a single agent.
- It is recommended in patients who can be initially treated with monotherapy (i.e., BP < 20/10 mmHg above goal BP) and who do not respond well to a moderate dose of antihypertensives. **Strategy**:
  - Switch to drug 2 (rather than increasing dose of drug 1 or adding a 2nd drug).
  - If this is ineffective, switch to drug 3.

Addition of a second drug:

- If sequential monotherapy is ineffective or unacceptable, use 2 or more drugs.
- Eventually, more than one drug is needed in patients initially controlled:

First-line Standard Combination Therapy in Hypertension

- Long acting (DHP) CCBs + long acting ACE inhibitor or ARB.

Combination Therapy, recommended if BP is > 20/10 mmHg above goal[53]:

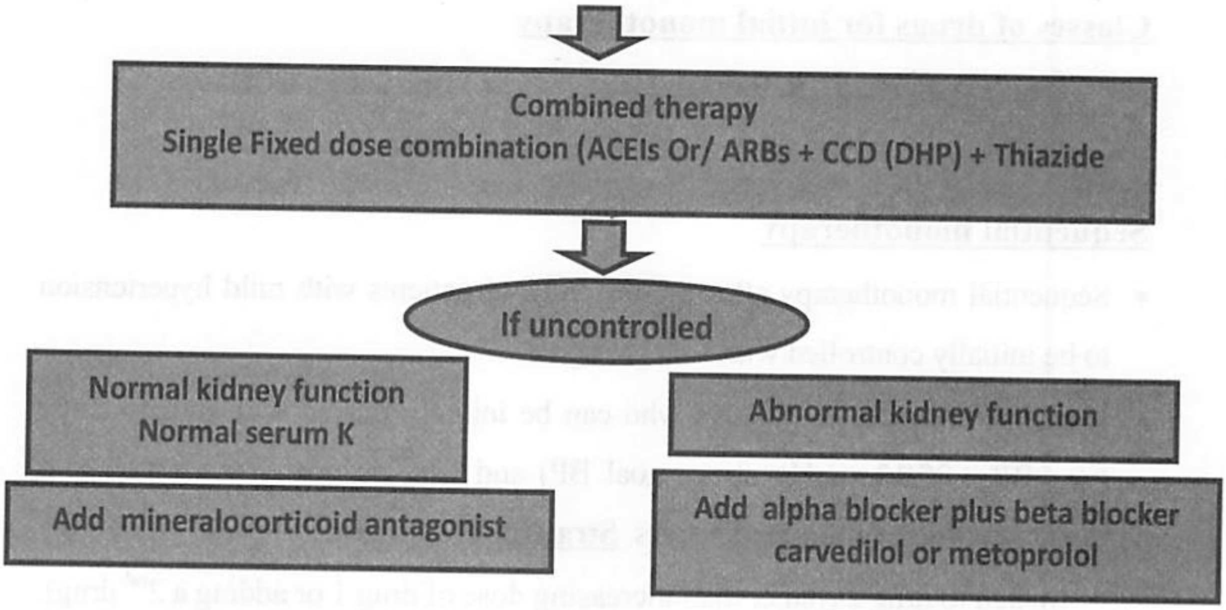
- If patient is using long-acting (DHP) CCB or a long-acting ACE inhibitor or ARB → add the second one.
- In patients on a thiazide diuretic→ discontinue the thiazide & start the standard combination therapy above.
- Preferred 2nd drugs in patients on βBs: thiazides or a (DHP) CCB.

---

[52] Other drugs (used in special situations): βBs without intrinsic sympathomimetic activity (e.g. in ischemic heart diseases), α_1-blockers (in prostatic obstruction), direct vasodilators e.g. hydralazine (eclampsia), nitroprusside (hypertensive emergencies), α-methyldopa (pregnancy).

[53] In non-obese already being treated with and doing well on combination of a thiazide diuretic & long-acting ACEI, replace thiazide with a long-acting DHP CCB. In obese, the combination of a thiazide diuretic and a long-acting angiotensin inhibitor can be continued.

Management of Resistant Hypertension


Combined therapy
Single Fixed dose combination (ACEIs Or/ ARBs + CCD (DHP) + Thiazide
If uncontrolled
Normal kidney function
Normal serum K
Abnormal kidney function
Add mineralocorticoid antagonist
Add alpha blocker plus beta blocker
carvedilol or metoprolol

Beneficial effects of drug combinations in hypertension

1. Additive combination therapy:

- ACEI + CCB (DHP or NON DHP).
- ARB+ CCB (DHP only) or βB + CCB(DHP).

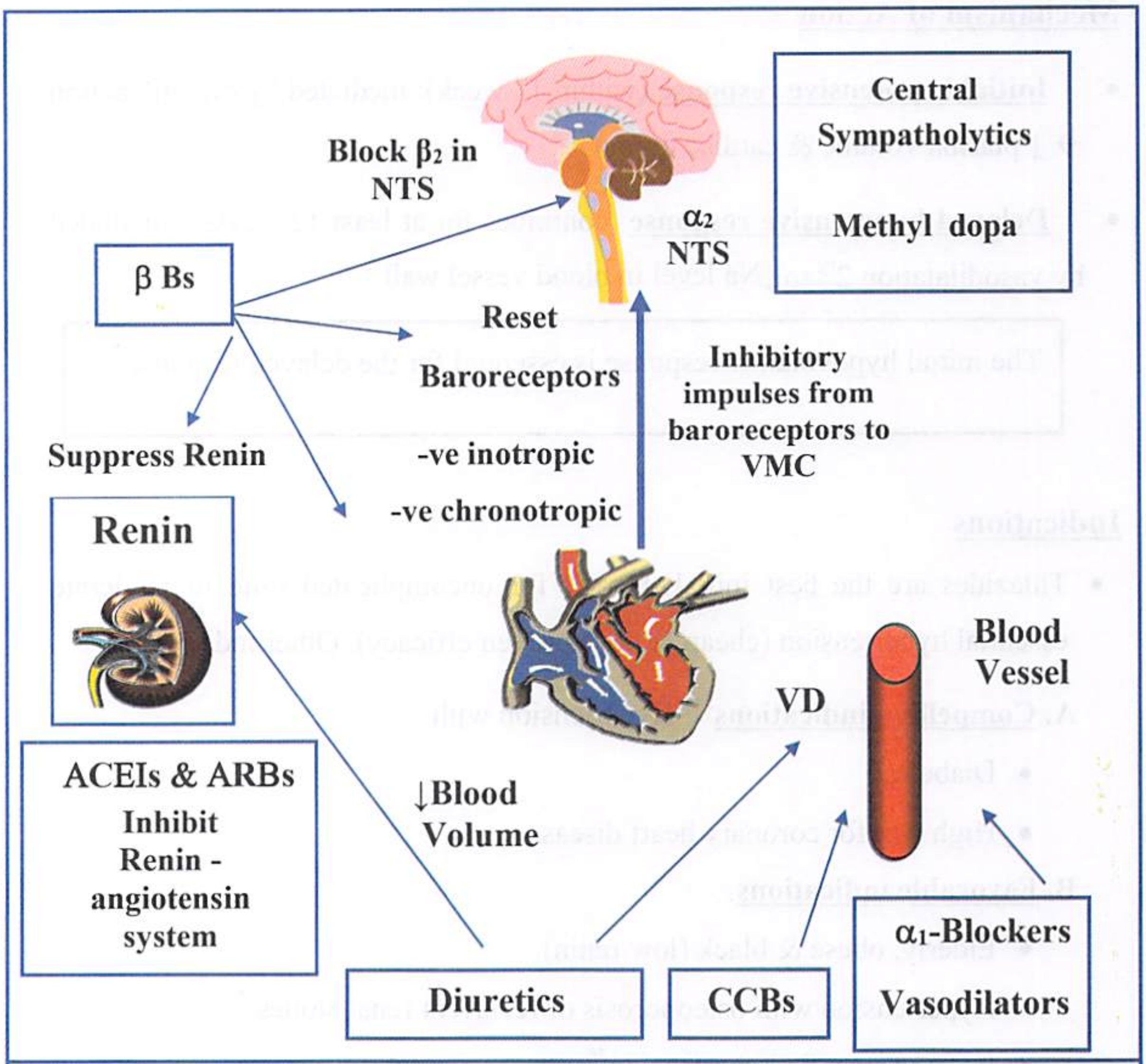
N.B.: in addition to the additive antihypertensive effect of βBs & CCBs, βBs also counteract the reflex tachycardia induced by CCBs.

2. Synergistic combination therapy

- **Thiazides plus βBs or thiazides plus ACEIs**
  - Thiazides synergize with most antihypertensives by decreasing volume expansion.

  Other synergistic mechanisms include:

  - Activation of renin-Ag system by thiazides potentiates βBs & ACEIs in obese, black & elderly; with low renin (βBs & ACEIs work mainly in high renin states).
  - Reduction in antihypertensive effect of diuretics, 2^{ry} to their activation of renin-Ag system, is counteracted by inhibitory effects of βBs, ACEIs or ARBs on the renin-Ag system.
  - ACEIs & ARBs neutralize metabolic effects of thiazides (βBs worsen them).


Central
Sympatholytics
Methyl dopa
Block β₂ in
NTS
α₂
NTS
β Bs
Reset
Baroreceptors
Inhibitory
impulses from
baroreceptors to
VMC
Suppress Renin
-ve inotropic
-ve chronotropic
Renin
Blood
Vessel
VD
ACEIs & ARBs
Inhibit
Renin -
angiotensin
system
↓Blood
Volume
α₁-Blockers
Diuretics
CCBs
Vasodilators

- BP is controlled at 4 sites: heart, blood vessels, kidney (renin - angiotensin system) & baroreceptors[♦]. ↑ BP above 120/80mmHg→ ↑ inhibitory impulses from baroreceptors to VMC → ↓ sympathetic activity→ ↓BP. In hypertension, baroreceptors are set at a level of BP > 120/80mmHg. βBs reset the baroreceptors.

Sites of Actions of Different Classes of Antihypertensive Drugs

---

[♦] Baroreceptors are continuously sending inhibitory impulses to VMC. If BP ↓below 120/80, fewer inhibitory impulses are sent to the VMC→ ↑sympathetic activity →↑BP. If BP ↑, the inhibitory impulses are ↑ to ↓ BP.

I. Thiazides Diuretics

Mechanism of Action

- **Initial hypotensive response** (within 1st week): mediated by diuretic action → ↓ plasma volume & cardiac output.
- **Delayed hypotensive response** (continues for at least 12 weeks): mediated by vasodilatation 2ry to ↓Na level in blood vessel wall.

The initial hypovolemic response is essential for the delayed response♦

Indications

- Thiazides are the best initial therapy for uncomplicated mild to moderate essential hypertension (cheap & have proven efficacy). Other indications:

A. **Compelling indications**[54]: Hypertension with

- Diabetes.
- High risk for coronary heart disease.

B. **Favorable indications**:

- Elderly, obese & black (low renin).
- Hypertension with osteoporosis or recurrent renal stones[55].
- Isolated systolic hypertension[56].

Adverse effects in antihypertensive doses

1. Sulfonamide hypersensitivity (absolute contraindication).
2. Impotence (relative contraindication).
3. Sleep disturbances.

N.B.: metabolic side effects may occur if used in high dose.

♦ Volume depletion → ↓ level of a central digitalis-like hormone → ↑ Na^+-K^+ ATPase activity → Na^+ is pumped out of smooth muscles (despite partial return of blood volume to baseline level).

[54] ↓ Mortality, CV complications & stroke.

[55] Thiazides given for > 2 years: ↓ Risk of fracture hip as they ↓ Ca^{++} excretion.

[56] Do not ↓ SBP by > 20 mmHg for fear of lowering the DBP → ↑ CV mortality.

Preparations

a. Low dose chlorthalidone 12.5-25 mg (& possibly indapamide):

- Longer acting thiazide analogue which is considered of choice[57].

b. Low dose hydrochlorothiazide: 6.25 - 25 mg/day

- Not associated with activation of the renin-angiotensin system[58]→ more effective than higher doses & even more effective than loop diuretics.
- Not associated with metabolic adverse effects.

c. Metolazone:

- More potent analogue useful in resistant hypertension 2^{ry} to volume expansion (e.g. renal impairment, high salt diet, long term use of vasodilators).

Thiazides or loop diuretics?

- Thiazides are preferred in mild to moderate non complicated essential hypertension but loop diuretics are needed in:
    - Fluid overload due to heart failure or renal disease.
    - Resistant hypertension (due to volume expansion)[59].

---

[57] It significantly reduced the risk of cardiovascular events and heart failure. It is superior in controlling systolic blood pressure esp. nocturnal blood pressure.

[58] Salt-sensitive hypertensives (with low renin level) as in elderly, black patients respond better to diuretics than to ACEIs & β-blockers (which act on renin-angiotensin system).

[59] Blood pressure above 140/90 mmHg in patients below age 60 and above 160/90 mmHg in those over age 60, despite intake of three or more antihypertensive medications.

II. β-Adrenergic Blockers

Mechanism of Action

- **β_1-blockade** (mainly)
  - Suppression of renin release (65%).
  - Negative inotropic & chronotropic effects (15%).
- **β_2 – blockade**
  - Central sympatholytic effect (block β_2 receptors in NTS →↓NE).
  - Peripheral sympatholytic effect (block presynaptic β_2 receptors →↓NE).
- Resetting of baroreceptors.
- Some β-blockers are vasodilators.

Advantages & Disadvantages

- Protect against coronary heart disease & ↓ CV mortality[60] .
- Do not protect against cerebrovascular events.
- Impair glucose tolerance & ↑ risk of new onset diabetes

Preparations

- Any βB can be used except those with intrinsic sympathomimetic activity[61].
- Vasodilator beta blockers are preferred e.g. carvedilol & nebivolol.

Indications (used less often for initial therapy in absence of a specific indication)

A. **Compelling indications**: in hypertension with

- Coronary heart disease (angina pectoris or post MI).
- Systolic heart failure.
- Atrial flutter/ fibrillation (if rate control is desired).

B. **Favorable indications**:

- Hypertension with: hyperthyroidism (high COP), essential tremors, migraine.
- Peri-operative hypertension.

---

[60] The observation that βBs after acute MI improved long-term survival raised the question of whether similar cardioprotection exists in hypertensives without clinical coronary disease. Three trials showed no benefit, one (metoprolol) showed benefit & one (atenolol) showed worsening.

[61] Selectivity of βBs has no place in choice since it is lost at antihypertensive doses.

III. Angiotensin-Converting Enzyme Inhibitors

Mechanism:

- Peripheral vasodilatation 2^{ry} to ↓ Ag-II and ↑ BK.
- ↓ Aldosterone secretion.

Indications:

A. **Compelling indications**: in hypertension with

- Systolic heart failure.
- IHD: high coronary disease risk & Post-MI.
- Diabetes mellitus.
- Proteinuric chronic renal failure.

ARBs are alternatives if ACEIs are not tolerated.

B. **Possible indications:**

- Hypertension 2^{ry} to unilateral renal artery stenosis.
- Hypertensive urgency.

N.B.: Aliskiren is a selective renin inhibitor, as effective as ACEIs or ARBs[62].

IV. Calcium Channel Blockers (CCBs)

Mechanism:

- Peripheral arterial vasodilatation and ↓total peripheral resistance.
- Diuretic action (↑ renal blood flow).
- ↓ Aldosterone secretion (prevent fluid retention).

Indications: no absolute indications in hypertensive patients

CCBs are alternatives to other drugs in:

1. Isolated systolic hypertension → alternative to thiazides.
2. Hypertension with migraine → alternative to βBs.
3. Hypertension with IHD, or AF (rate control) → alternative to βBs.
4. Hypertension with asthma or peripheral vascular diseases (worsened by βBs).

---

[62] Aliskiren should not be combined with ACEIs or ARBs. May induce, diarrhea, cough, angioedema (less often than ACEIs). Metabolized by CYP 3A4 → many drug interactions, CI in pregnancy.

Preparations

- Amlodipine (long acting).
- SR- preparations of short acting agents[63].

Standard Combination Therapy in Hypertension

- Long acting (DHP) CCBs + long acting ACE inhibitor or ARB.

Other antihypertensives

I. Central Sympatholytics (see adrenergic system)

A. Methyldopa:

- α_2 agonist; antihypertensive especially in pregnancy.

B. Clonidine:

- α_2 & imidazoline receptor agonist used in hypertensive urgencies.

II. α_1- selective blockers (prazosin - doxazosin)[64](see adrenergic system)

- They are not 1st choice in any type of hypertension as they induce postural hypotension, tachycardia & fluid retention → tolerance.
- Mainly used in essential hypertension with benign prostatic hypertrophy.

III. Direct vadodilators (see CHF)

- Hydralazine: used in eclampsia.
- Nitroprusside: used in hypertensive emergencies.

---

[63] Long acting agents of CCBs are used, since short acting agents → ↑ HR due to reflex sympathetic stimulation → myocardial ischemia & ↑ mortality.

[64] Phentolamine & phenoxybenzamine are nonselective α blockers used in pheochromocytoma (not in hypertension as they induce excessive reflex tachycardia→↑ BP (tolerance to antihypertensive effect).

CHOICE OF ANTIHYPERTENSIVES

	Recommended Drugs	**Drugs better to be avoided**
Pregnancy • **Early** • **Labor (eclampsia)**	• α-methyldopa (of choice). • Labetalol. • Nifedipine (long acting) • Labetalol - Hydralazine.	• ACEIs -ARBs: teratogenic, fetotoxic. • Diuretics → ↓ blood volume.
Diabetes	• **Low dose** thiazide. • ACEIs or ARBs: reno-protective, improve glucose tolerance.	• βBs → mask symptoms of hypoglycaemia & delay recovery. • **Full dose** thiazides → ↑glucose.
Asthma **COPD**	• CCBs: (relax bronchi). • ACEIs (→ cough) or ARBs. • Thiazide diuretics.	• βBs (especially, non-selective) → bronchospasm.
Angina[65]	• βBs (of choice). • CCBs (favourable effect). • ACEIs or ARBs.	• βBs in vasospastic angina.
Systolic HF	• ACEIs (or ARBs) – diuretics. • Spironolactone /eplerenone if renal function is preserved). • β blockers: for stable cases.	• βBs in de-compensated HF. • Verapamil or diltiazem.
Chronic kidney disease	• ACEIs or ARBs (if renal function is preserved). • Loop diuretics. • CCBs.	• ACEIs, ARBs & K^+ sparing diuretics in severe renal impairment.
PVD	• CCBs.	• βBs.
Isolated systolic hypertension	• Thiazide diuretics. • CCBs.	
Lactating women	• Enalapril- captopril-benzapril. • Metoprolol –atenolol- labetalol. • Methyldopa –nifedipine. • Spironolactone- thiazides	• Other ACEIs- ARBs. • Amlodipine. • Thiazides in large dose.

---

[65] For post MI: βBs - ACEIs (for systolic dysfunction) – spironolactone (aldosterone antagonists).

HYPERTENSIVE CRISIS

Hypertensive Urgencies

- Severe ↑ in BP (systolic > 220 mmHg and/or diastolic BP > 120 mmHg) without TOD in relatively asymptomatic patient.
- It can be managed with oral drugs with relatively rapid onset of action[66].
- **Drugs used**: frusemide, captopril, atenolol.

Hypertensive emergencies

- Severe ↑ in BP (systolic > 220 mmHg and/or diastolic BP > 120 mmHg) with acute progressive TOD & life threatening complications e.g. hypertensive encephalopathy[67]. It requires IV drugs.

A. In most H. Emergencies

- Nitroprusside.
- Nicardipine (except acute heart failure).
- Labetalol (except acute heart failure).
- Fenoldopam (except in glaucoma).

B. In specific H. Emergencies

- Nitroglycerine: in acute coronary syndrome.
- Esmolol: in aortic dissection and perioperative hypertension.
- Phentolamine: in excess CA (pheochromocytoma, clonidine withdrawal...).
- Enalaprilat: in acute left ventricular failure.

---

[66] In previously treated patients control BP by reinstitution of drug if patient is not adherent to treatment or ↑ dose if adherent to treatment. Restricting salt intake ± diuretic may be enough in patients with ↑ Na^+ intake.

[67] Neurological signs: confusion, headache, visual disturbances, vomiting and convulsions.

DRUG THERAPY OF-ARRHYTHMIA

Types of cardiac tissue based on electrophysiological properties

I. Non-automatic tissue: Atria & Ventricles

- Non-automatic tissue cannot initiate an impulse but is excitable i.e. can respond to an adequate impulse by generating an action potential.

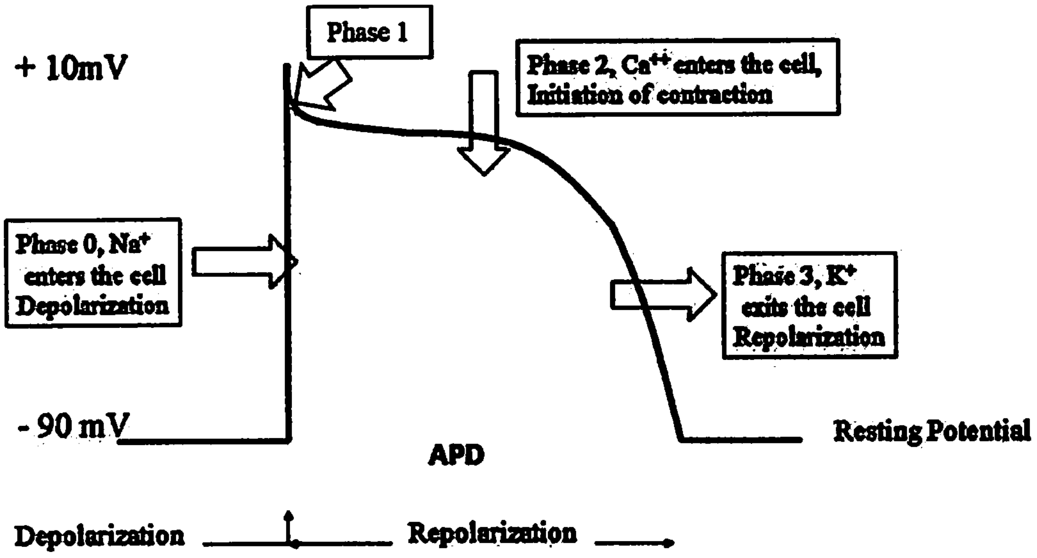
II. Automatic tissue: SAN, AVN, Purkinje fibres

- Automatic tissue can initiate an impulse which excites the rest of the heart.

Phases of cardiac action potential

I. Non-automatic Tissue

- During diastole, contractile tissue has a resting membrane potential ≈ - 90 mV i.e. it is in a polarized state with inside of the cells -ve relative to outside.
- Arrival of an impulse from automatic tissue depolarizes the membrane to -70 mV which briefly opens Na^+ channels. Entry of Na^+ into cells elevates the potential to +30 mV (phase 0).
- Phase 1 is due to K^+ outflux. This is followed by a plateau (phase 2) due to opening of Ca^{++} channels when the potential exceeds -55 mV; influx of Ca^{++} is prolonged but is of small magnitude so that it is balanced by the already existing K^+ outflux. Finally, membrane is repolarized (phases 3) when Ca^{++} channels close due to unopposed outflux of K^+.


Phase 1
+ 10mV
Phase 2, Ca++ enters the cell, Initiation of contraction
Phase 0, Na+ enters the cell Depolarization
Phase 3, K+ exits the cell Repolarization
- 90 mV
APD
Resting Potential
Depolarization
Repolarization

II. Automatic Tissue (SAN – AVN – Purkinje)

- During phase 4 (diastole), the membrane of automatic tissue undergoes spontaneous diastolic depolarization due to an inward pacemaker current (slow Ca^{++} current in SAN/AVN or fast Na^+ current in Purkinje fibers) which overcomes an outward decaying K^+ current.
- Phase 0 is triggered in Purkinje fibers when membrane potential reaches threshold (-70 mV) as in non automatic fibers. However, phase 0 in SAN & AVN is triggered at -55mV & is slower to rise (depends on slow Ca^{++} influx).
- SAN has the greatest slope of diastolic depolarization →fastest to reach threshold, thus, it is the pacemaker from which the impulse is triggered & propagates through the AVN to His bundle & Purkinje system to stimulate all of the ventricular tissue, simultaneously.

Important Terms

APD: action potential duration - **ERP**: effective refractory period.

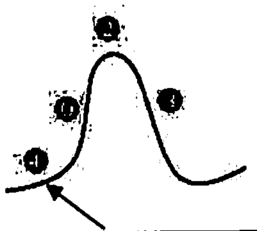
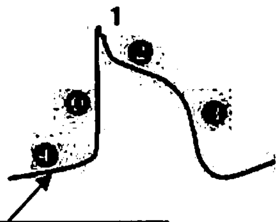
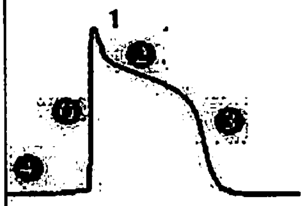
- During the APD, the heart is refractory since the depolarizing potential during the APD inactivates sodium[68] & Ca^{++}channels.
- The **ERP** is slightly longer than APD. It can be ↑ by:
  - ↑ APD e.g. K^+-channel blockers.
  - Blocking Na^+ & Ca^{++} channels e.g. Na^+ channel blockers in Purkinje fibers & CCBs & β-blockers in AVN.

---

[68] Voltage-gated Na^+ channel has an inner h-gate & outer m-gate. It exists in 3 states:
1. **Activated**: both h & m - gates are open during phase 0 to initiate AP.
2. **Inactivated**: m-gate open, h-gate closed during the rest of the AP; it cannot respond to a stimulus as h-gate is voltage independent.
3. **Resting**: inner h-gate open & outer m-gate closed. It can respond to depolarization (-70 mv) as its m-gate is voltage-dependent.

Phases of Cardiac Action Potential

Important Parameters & Their Significance

	Slow Automatic SAN & AVN	**Fast Automatic Purkinje**	**Non-automatic Atrial & ventricular**
Phase Parameter & its significance	 Slow diastolic depolarization		 Resting potential
	Mechanism		
Phase 0 **V_{max}→ Conductivity**	• Slow Ca^{++} influx	• Fast Na^+ influx	• Fast Na^+ influx
Phase 2; Plateau **APD → ERP**	• Absent	• Balance of inward Ca^{++} & outward K^+ current	
Phase 3 **APD → ERP**	• Outward K+ efflux		
Phase 4 • Slope of phase 4 ↑ slope → enhanced automaticity	• Slow diastolic depolarization due to a pacemaker **Ca^{++} current** overcoming an outward K^+ current	• Slow diastolic depolarization due to a pacemaker **Na^+ current** overcoming an outward K^+ current	• Resting potential due to balance between inward Na^+& outward K^+ currents.

N.B.: Phase 1 is due to K^+ outflux or Cl^- influx (it is absent in SAN & AVN).

Vmax = maximum slope of phase 0: determines conduction velocity: drugs decreasing Vmax delay conduction, e.g. Na^+-channel blockers in Purkinje; adenosine, CCBs & βBs in AVN.

Mechanisms of Arrhythmia

I. Disturbance in impulse generation

1. Disturbed automaticity of automatic tissue:

- ↑ Sympathetic activity (anxiety, thyrotoxicosis) → ↑ Ca^{++} influx → ↑ slope of diastolic depolarization → sinus tachycardia
- ↑ Vagal tone (digoxin toxicity) → ↑ K^{+} outflux → ↓ slope of diastolic depolarization → sinus bradycardia.

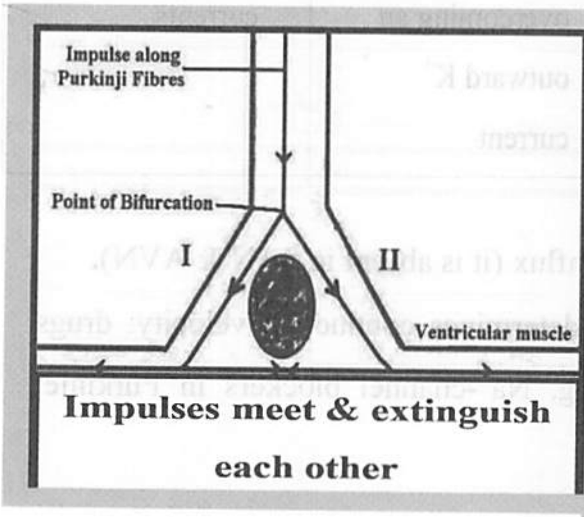
2. Automaticity in non-automatic tissue [ectopic pacemaker; slow responses]

- Ischemia initiates abnormal ionic currents in non-automatic tissue.

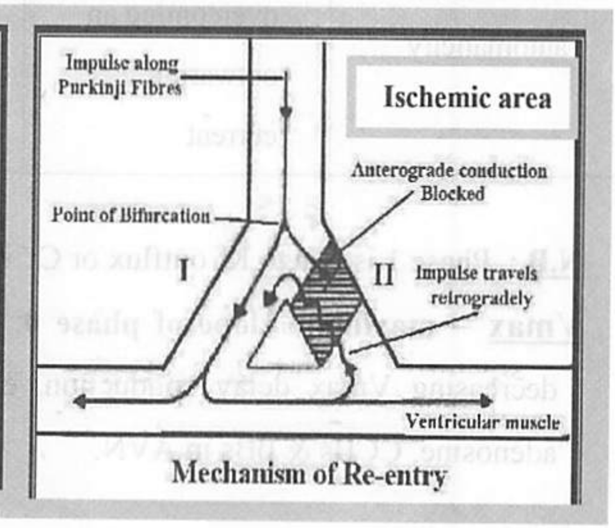
II. Disturbance in impulse conduction: heart block – re-entry arrhythmia

Re-entry Arrhythmia:

- In a normal heart, impulses move in one direction & cannot return to close a circuit. Impulses passing in opposite directions along 2 pathways (I, II) are conducted at equal velocities → meet, extinguish one another & die out, never returning to the point of origin.
- Re-entry (circus movement) occurs if continuous circulation of an impulse occurs (due to difference in conduction velocity or refractoriness between the 2 pathways, e.g. due to ischemia) allowing one impulse to re-enter point of origin & re- excite heart → paroxysmal arrhythmias whose rate depends on the number of times the impulse passes through circuit before it dies out.


Impulse along Purkinji Fibres
Point of Bifurcation
I
II
Ventricular muscle

Impulses meet & extinguish each other


Impulse along Purkinji Fibres
Ischemic area
Anterograde conduction Blocked
Point of Bifurcation
I
II
Impulse travels retrogradely
Ventricular muscle

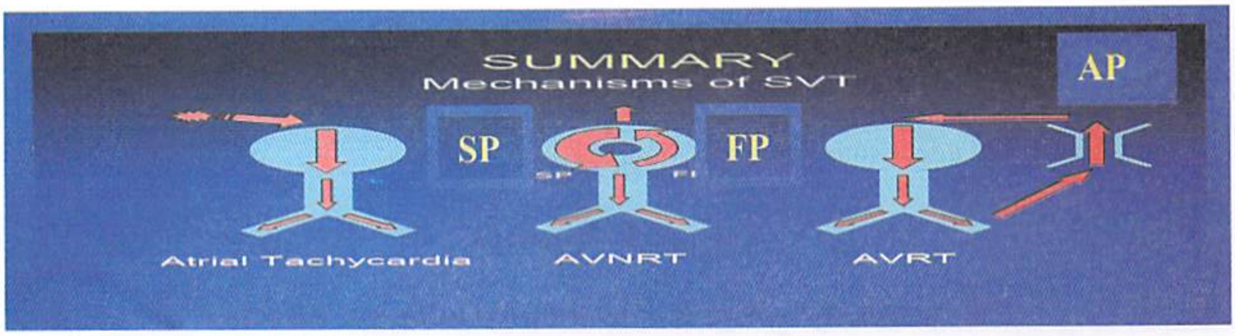
Mechanism of Re-entry

Examples of re-entry arrhythmias:

- Ventricular tachycardia, atrial flutter (AF), atrial fibrillation (AF).
- Paroxysmal supraventricular tachycardia (PSVT). PSVT is either:

a. **AV nodal reentrant tachycardia (AVNRT):** Re-entrant circuit is in AVN

- AVN is divided into a fast & a slow pathway. A premature beat finds fast pathway refractory, passes in slow pathway (SP) to ventricles & passes retrogradely to atria in fast pathway (FP) which by now has recovered from refractoriness.

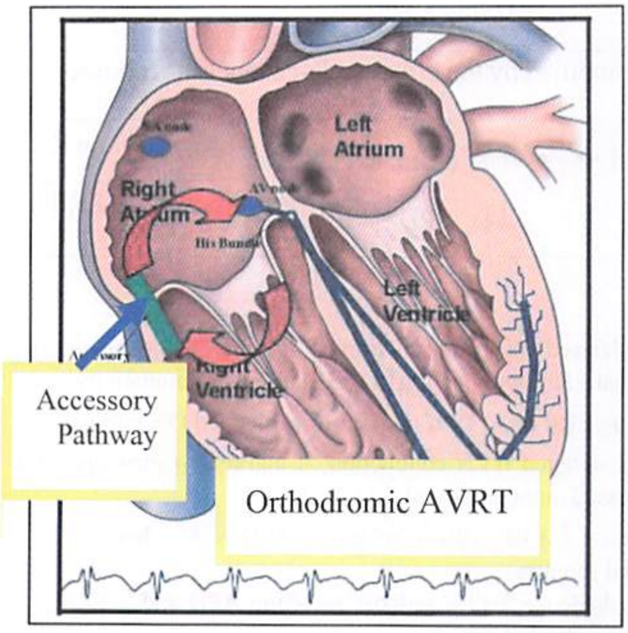

SUMMARY
Mechanisms of SVT
SP
FP
AP
SP
FI
Atrial Tachycardia
AVNRT
AVRT

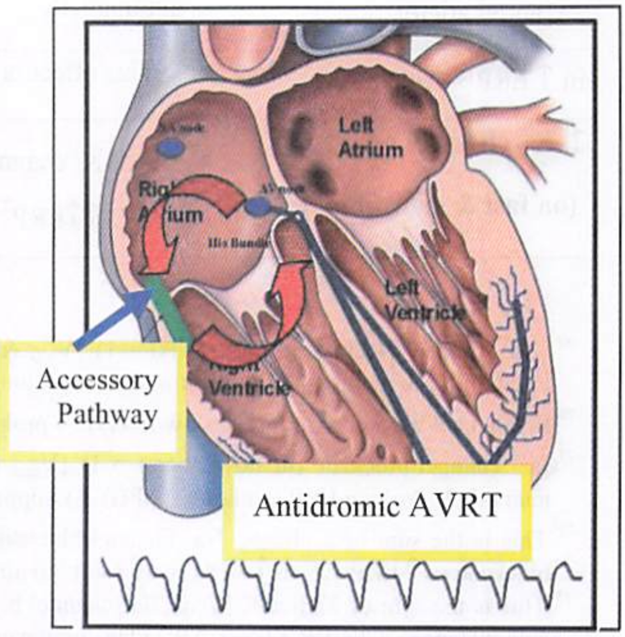
b. **Atrio-ventricular re-entrant tachycardia** (AVRT): e.g., WPW syndrome

Re-entrant circuit is at atrio- ventricular junction with a slow pathway in AVN & a fast accessory pathway (AP) connecting atria with ventricles. There are 2 types:

i. Orthodromic: atrial impulse passes in AVN & quickly re-enters atrium via AP.

ii. Antidromic: impulse created in the atrium. & travels down AP and pre-excites the ventricles retrogradely & back to atria via AVN.


Left Atrium
Right Atrium
AV node
His Bundle
Left Ventricle
Right Ventricle
Accessory Pathway
Orthodromic AVRT


Left Atrium
Right Atrium
AV node
His Bundle
Left Ventricle
Right Ventricle
Accessory Pathway
Antidromic AVRT

Antiarrhythmic Drugs

Vaughan Williams classification

Class I: Na$^+$-channel blockers[69].

- **Class Ia: procainamide**, quinidine, , disopyramide
- **Class Ib: lidocaine**, phenytoin, mexiletine, tocainide,
- **Class Ic: propafenone**, flecainide, encainide

Class II: β-blockers.

Class III: K$^+$-channel blockers[70]: **amiodarone,** sotalol, ibutilide.

Class IV: Ca^{++} channel blockers[71]: **verapamil** and diltiazem.

Non-classified: adenosine – digoxin – magnesium sulfate.

All can be given orally **except** lidocaine- esmolol - adenosine- ibutilide.

Class I Agents

Pharmacodynamic & Electrophysiological effects

	Class Ia	**Class Ib**	**Class Ic**
	Procainamide	**Lidocaine**	**Propafenone**
1. Na$^+$ channel Blockade (on fast fibers): i. ↓ V_{max} & delay conduction. ii. ↓ phase 4 slope →↓automaticity	• Moderate dissociation rate→ moderate conduction block &↓ automaticity.	• Rapid Dissociation from normal tissue→ minimal effects on normal conduction.	• Slow dissociation → marked conduction block &↓ automaticity.
iii ↑ ERP/ ~APD	This effect is modified by the effect on K-channels as follows		
2. K$^+$ channel effect (on fast & slow fibers)	• Block K$^+$ channel → ↑ APD/↑↑ERP[72]	• ↑ K$^+$efflux → ↓↓ APD>↓ ERP[73]	• No effect on K$^+$ → ~ APD /↑ERP[74]

---

[69] Na $^+$ channel blockade (in fast fibers) →1) ↓V_{max} & delayed conduction; if marked → wide QRS duration. 2) ↓ Excitability & membrane stabilization 2ry to prolonged ERP (without ↑ APD). 3) Suppress automaticity.

[70] K$^+$-channel blockade (in fast & slow fibers) → prolong ERP & APD; if marked → prolonged QT interval.

[71] Ca^{++} channel blockade (in slow fibers)→ 1) ↓V_{max} & delayed AVN conduction; if marked → prolonged PR interval. 2) Prolong ERP (without ↑ APD). 3) Suppressed automaticity of SAN (↓ HR)

[72] This is the sum of 2 effects: Na' channel blockade → ↑ ERP without affecting APD & K$^+$ channel blockade →↑ ERP 2^{ry} to ↑ APD (very useful in atrial re-entry).

[73] This is the sum of 2 effects: Weak Na$^+$ channel blockade → ↑ ERP without affecting APD and ↑ K$^+$ conductance → ↓ ERP 2^{ry} to ↓ APD (This may worsen atrial re-entry).

[74] Propafenone has additional Ca Channel blocking activity 2ry to beta adrenoceptors blockade

Class Ia Agents

Procainamide & Quinidine

- **Pharmacodynamics** (Class Ia; see before)
- **Autonomic Effects**

1. **Antimuscarinic:** paradoxical ventricular tachycardia in atrial flutter & fibrillation→↑ AVN conduction (more with quinidine) → blocked by adding digitalis, β Bs or verapamil.
2. Ganglion blockade with procainamide.
3. α-blockade with quinidine

Therapeutic Uses

- Broad-Spectrum → ventricular & SV arrhythmias including WPWS.

N.B.: Procainamide has largely replaced quinidine due to the increased risk of "Torsade de Pointes" & excessive antimuscarinic effects of quinidine.

Adverse Effects

1. **Cardiotoxicity**
    - Hypotension (ganglion blockade with procainamide & α-blockade with quinidine).
    - Slowing of conduction & myocardial depression.
    - "Torsade de Pointes" arrhythmia (↑ QT) → syncope (more with quinidine).
2. Thromboembolism[75] - thrombocytopenia.
3. **Systemic lupus** (with procainamide limits its long term use).
4. **Cinchonism**: tinnitus, loss of hearing, blurred vision (with quinidine).
5. GIT: diarrhea, nausea and vomiting.

Disopyramide (Class Ia)

- Broad spectrum, similar to procainamide & quindine with marked negative inotropic (→ HF) & antimuscarinic effects → glaucoma, urine retention.

---

[75] Stagnation of blood in atria in long standing AF (without heparin) → thrombus formation & showers of emboli on return to sinus rhythm & improvement of contractility.

Class Ib Agents

I. Lidocaine (local anesthetic & anti-arrhythmic)

Pharmacodynamics: Class Ib (see before)

- Lidocaine has minimal effects on normal tissue but selectively blocks inactivated sodium channels in ischemic, depolarized tissue → marked conduction block & ↓automaticity.

Uses: Ventricular arrhythmias

- Selective on ischemic & depolarized tissues[76] thus it is used in:
  1. V. tachycardia in cardiac surgery or M. infarction (least cardiotoxic).
  2. Digitalis-induced arrhythmia (does not ↑ digoxin level → safe).

N.B.: it is ineffective in atrial flutter & fibrillation (as it ↓ ERP) & in PSVT [77] as it has no effect on AVN conduction

Dosage (it is ineffective orally due to extensive 1st-pass metabolism)

- IV bolus followed by maintenance infusion as it has very short t½

Adverse Effects

1. Cardiac: it is the least cardiotoxic anti-arrhythmic drug, but still it may precipitate cardiac arrest or worsen impaired conduction in diseased hearts.
2. CNS: perioral parasthesias, dizziness, tremors, **convulsions**.

II. Mexiletine & Tocainide (Class Ib)

- They are lidocaine congeners with minimal 1st pass metabolism (so-called oral lidocaine). Their toxicities limit their usefulness

III. Phenytoin (Class Ib)

- An antieplipetic drug that can be used in digitalis – induced arrhythmia.

---

[76] Na^+ channels are deactivated → outer gate open → ↑ lidocaine binding → ↑effect.

[77] Dangerous →↓ ERP of atria & accessory pathway→↑ rate of re-entrant tachycardia e.g. PSVT, AF.

Class Ic Agents

Propafenone

Pharmacodynamics:

- Class Ic (see before).
- Beta blocking effect.

Therapeutic uses

1. SV arrhythmias (AF; Af and PSVT)
2. Ventricular arrhythmias (resistant cases).

Adverse effects:

1. Arrhythmias – A-V block – heart failure.
2. Taste disturbances, constipation.
3. Bronchospasm.
4. Dizziness - blurred vision

Class II Agents

β-Adrenoceptor Blockers

Propranolol - Esmolol - Atenolol

Pharmacodynamics

Block β-adrenoceptors → block intrinsic sympathetic activity in slow fibres:

- ↓ SAN & AVN activity.
- ↓ Phase 4 slope in pacemakers (slow automaticity).

Therapeutic uses: broad spectrum

1. Arrhythmias due to sympathetic overactivity: exercise, emotion, anesthesia, thyrotoxicosis, pheochromocytoma.
2. Arrhythmias following myocardial infarction→↓ mortality.
3. IV esmolol can be used for termination of PSVT.

Class III Agents

A. Amiodarone

Pharmacodynamics: blocker of K^+, Na^+ & Ca^{++} channels and β- blocker:

K^+ channel blockade (main): delays repolarization →↑APD & ERP in all cardiac tissue & accessory tracts→ blocks reentry arrhythmia (PSVT, AF, Af).

Na^+ channel blockade: suppresses ectopic pacemaker (↓ phase 4 slope) & slows conduction (↓Vmax in fast fibres).

CCB → coronary & peripheral vasodilation, ↓ sinus rate & AVN conduction.

Therapeutic Uses:

Broad-Spectrum → ventricular & SV arrhythmias, including WPWS.

Kinetics & Dosage (long $t_{½}$; 35-103 days)

- Full effect is reached after a lag period of 1-3 weeks → given as a loading dose followed by maintenance dose (oral or IV)
- Displaces digoxin from plasma proteins → ↑toxicity.

Adverse Effects: **Cumulative** in most tissues

1. Cardiac: bradycardia, heart block, hypotension (less risk of Torsade de Pointes).
2. Corneal micro deposits (asymptomatic).
3. Hypo- or hyperthyroidism (heavily iodinated)
4. ↑ Liver enzymes.
5. Pulmonary infiltrates & fibrosis.
6. Peripheral neuropathy & myopathy.
7. Photosensitivity.

Precautions

- Chest x ray/ 3 months.
- Liver functions/ 6 months.
- Thyroid functions/ 6 months.

Dronedarone:

- Related to amiodarone but devoid of iodine → minimal toxicity.
- Therapeutic uses: similar to amiodarone.

B. Sotalol

Action: nonselective β- blocker with class III antiarrhythmic effect.

Uses: ventricular arrhythmias - maintenance of rhythm in AF& Af.

Adverse Effects:↑ risk of "Torsade de Pointes"(limits use to serious arrhythmias).

Class IV Agents

Verapamil & Diltiazem

Pharmacodynamics:

Block Ca^{2+} current in **slow fibres**

- ↓ SAN & AVN activity.
- ↓ Phase 4 slope in pacemakers (slow automaticity).

Uses: Supra ventricular arrhythmias

1. AF & Af: prevents transmission of high atrial rate to ventricle (blocks AVN).
2. Termination of PSVT.

Side Effects

1. Paradoxical acceleration in AF associated with WPW syndrome → blocks conduction in AVN but not in fast accessory pathway (AP) → transmits high atrial rate to ventricles.
2. Adverse effects of CCBs (see before)

Adenosine

Pharmacodynamics

- Binds A_1 receptors → opens K^+ channel → hyperpolarization → ↓ Ca^{2+} influx →
  a. SAN →↓ rate.
  b. AVN →↓ conduction velocity - ↑ ERP → **Terminates PSVT**.
- Dilates coronary & peripheral blood vessels.

Uses: Terminates PSVT

Dosage: rapid IV bolus; may be repeated once after 1-2 minutes (ultra short; $t_{½}$:15 s).

Side Effects (transient)

1. Chest pain & dyspnea (A_1 receptors; bronchospasm **CI** in asthma).
2. Headache flushing (A_2 receptors; vasodilation).
3. Sinus bradycardia, arrest or AV block (**CI** in AV block).

Magnesium sulfate

Pharmacodynamics

- Natural physiologic competitive Ca antagonist at L - calcium channels:
  - Slows SAN rate.
  - Prolongs conduction time in myocardial tissue.

Uses: Given IV in

- Digitalis induced arrhythmia associated with hypomagnesemia.
- Torsades de pointes.

Choice of Antiarrhythmic Drugs

Broad therapeutic classification of anti-arrhythmic drugs:

- Lidocaine; phenytoin or mexilitine: **used in V. arrhythmias.**
- Verapamil, adenosine, digoxin: **used in SV arrhythmias.**
- Class 1a & 1c, βBs, amiodarone, sotalol: **Broad-spectrum.**

Atrial flutter (Af) & fibrillation (AF): DC in unstable hemodynamics

1. **Pharmacologic cardioversion** (class Ic, III, Ia):
   - Propafenone (best for atrial fibrillation).
   - Ibutilide (best for atrial flutter) [78].
   - Procainamide, quinidine, (+ digoxin, βBs or verapamil to block AVN).
2. **Maintenance of rhythm after conversion**[79]
   - Propafenone (+ verapamil), flecainide.
   - Amiodarone – sotalol.
   - βBs.
3. **Ventricular rate control** (block AVN)):
   - βBs - verapamil/ diltiazem - digoxin (if there is HF).
4. **Anticogulants**: to avoid thromboembolism.

---

[78] Dofetilide is also best for atrial flutter.

[79] Quinidine may be used.

PSVT[80]

- Adenosine or verapamil (1st choice).
- βBs & procainamide IV (2nd choice).

Ventricular Tachycardia: DC in unstable patients; if stable, give IV→

1. Amiodarone. } 1st & 2nd choices
2. Lidocaine. }
3. Procainamide - sotalol (provided left ventricle function is normal)

Bradycardia:

- Atropine (best).
- Cardiac pacing (if atropine fails).
- Isoprenaline.

Cardiovascular agents for lactating women

- Methyldopa
- Nifedipine (avoid amlodipine)
- Spironolactone
- Hydrochlorthiazide small dose (avoid thiazides in large dose)
- Enalapril- captopril-benzapril (avoid other ACEIs and ARBs)
- Metoprolol –atenolol- labetalol
- Quinidine - procainamide
- Lidocaine
- Verapamil
- Digoxin

---

[80] Procainamide → 1st choice in antidromic AVRT. Drugs blocking slow AVN are used in orthodromic but avoided in antidromic if diagnosis is uncertain, since ECG changes may not distinguish this arrhythmia from V. tachycardia. If case is V. tachycardia it will degenerate into fibrillation due to shortening of ventricular ERP by these drugs especially adenosine & digoxin. Moreover, if AF is concomitantly present; AVN block →↑ conduction across fast AP → V. fibrillation.

III. BLOOD PHARMACOLOGY

Intended Learning Outcomes (ILOs)

By the end of this chapter, the student should be able to:

- Identify the 3 major drug groups (antiplatelets, anticoagulants and fibrinolytics) involved in management of thrombotic diseases and compare their utilty in venous & arterial thrombosis.
- Differentiate between the 3 main groups of anticoagulants, their mechanisms, adverse effects, control of therapy and available antidotes.
- Explain why warfarin has a delayed onset of action and how this relates to the anticoagulation protocol.
- Explain the problems encountered with warfarin therapy and how the availability of other groups of anticoagulants reduced such problems.
- Discuss the choices of different anticoagulants in patients with liver or renal diseases
- Diagram steps of platelet aggregation & show the site of action of different antiplatelet drugs.
- Explain how specific fibrinolytics offer advantages over non specific agents.
- List 3 drugs used in management of excessive bleeding.
- List the main groups of hypolipidemic agents & discuss the value of combination therapy and mention rational combinations & undesirable ones.
- Name the 2 most common types of nutritional anemias and their causes.
- List the preparations of iron & vitamin B_{12} used in therapy.
- Identify drug groups inducing hematological disorders as well as those used in management of such disorders.

BLOOD PHARMACOLOGY

DRUG THERAPY OF THROMBOSIS

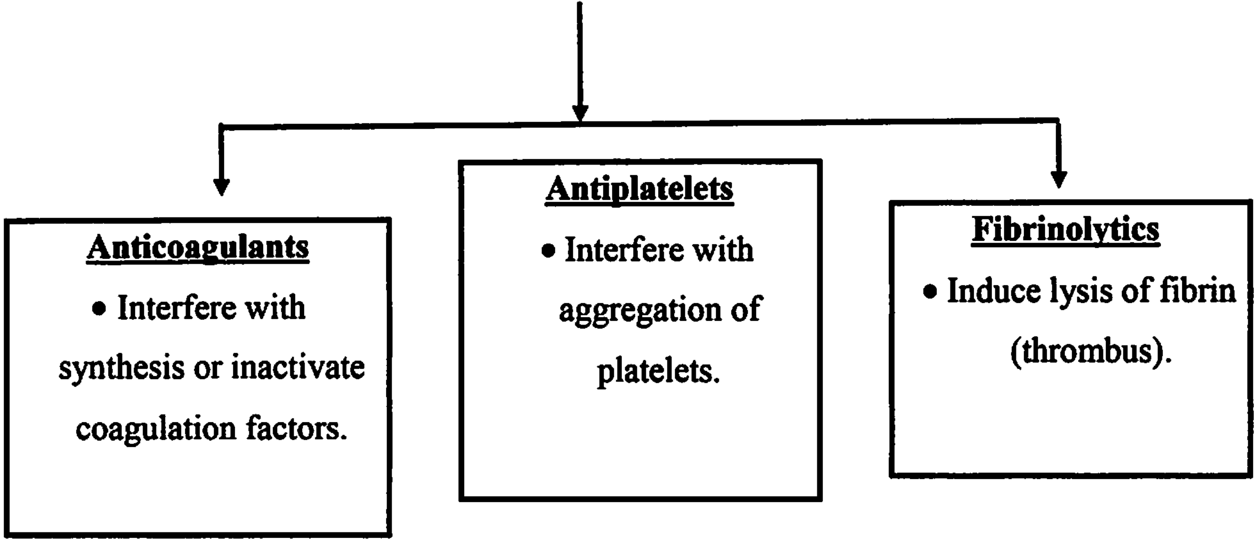
Thrombosis

- Thrombosis is a pathological condition resulting from inappropriate activation of the hemostatic mechanisms i.e. platelet aggregation & coagulation (fibrin formation).

Types of thrombi

- **Arterial (white) thrombus**: formed mainly of platelets (in a fibrin mesh). It is associated with atherosclerosis and can interrupt blood flow resulting in ischemia or death of tissue (infarction). → **managed mainly by antiplatelets & fibrinolytics.**
- **Venous (red) thrombus**: formed mainly of a fibrin tail with a white head (few platelets) . It is associated with stasis of blood. It may detach and travel resulting in emboli (e.g., deep venous thrombosis in lower limb → pulmonary embolism) → **managed mainly by anticoagulants.**

Drugs used in Management of Thrombotic Disease



Anticoagulants

- Interfere with synthesis or inactivate coagulation factors.

Antiplatelets

- Interfere with aggregation of platelets.

Fibrinolytics

- Induce lysis of fibrin (thrombus).

ANTICOAGULANTS

Coagulation

- Clotting factors are synthesized in liver and are present in an inactive form in the circulation. They are inactivated by antithrombin (natural anticoagulant).
- Stimulation of the coagulation cascade (by tissue factors from injured tissue & mediators on surface of platelets)→ sequential activation of clotting factors finally forming factor **Xa** .
- Factor **Xa** activates prothrombin (factor II) → thrombin (factor **IIa**).
- Thrombin catalyses hydrolysis of fibrinogen → fibrin (incorporated in clot).
- Cross linking of fibrin strands stabilizes clot →hemostatic platelet- fibrin plug.
- The fibrinolytic system is activated simultaneously (plasminogen→ plasmin→ fibrinolysis) in order to dissolve the clot (thrombus).

Classification of Anticagulants

A. Parentral anticoagulants:

I. Indirect thrombin inhibitors: Heparin – LMWHs.

II. Indirect selective inhibitor of factor Xa: fondaparinux.

III. Direct thrombin inhibitors: argatroban - bivalirudin - desirudin.

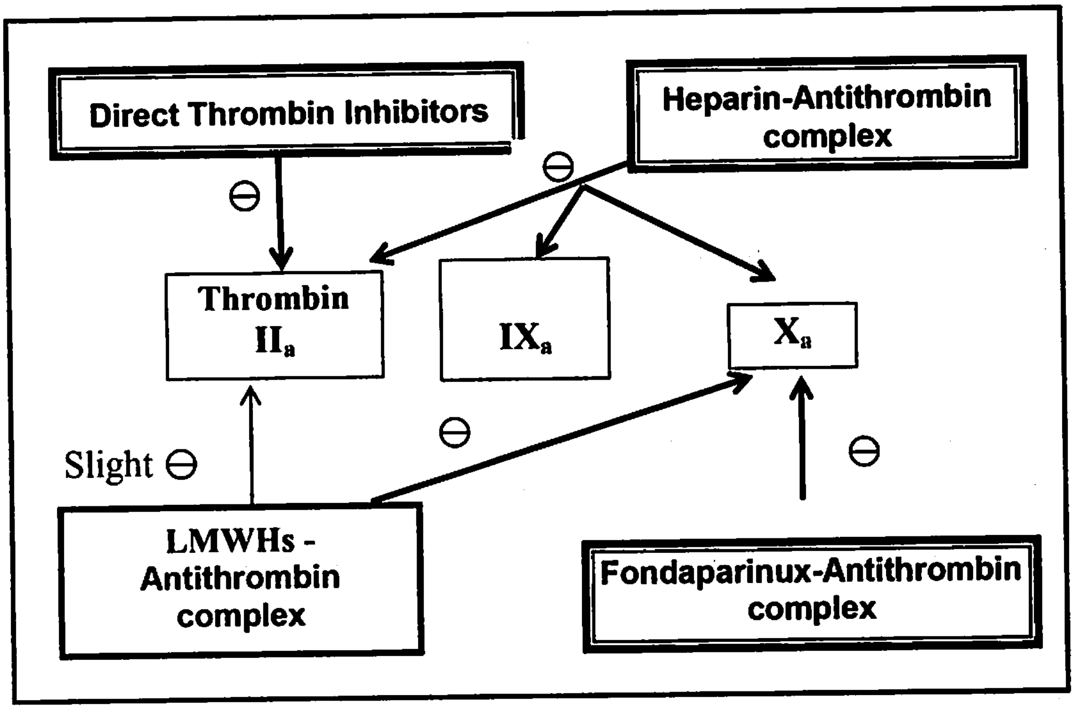
B. Oral anticoagulants:

I. Warfarin: inhibitor of synthesis of clotting factors (II, VII, IX, X).

II. New oral anticoagulants (NOAC)

1. Direct thrombin inhibitor: **Dabigatran.**
2. Direct inhibitors of factor Xa: **Rivaroxaban- apixaban.**

A. Parentral Anticoagulants


Direct Thrombin Inhibitors
Heparin-Antithrombin complex
⊖
⊖
Thrombin IIa
IXa
Xa
Slight ⊖
⊖
⊖
LMWHs - Antithrombin complex
Fondaparinux-Antithrombin complex

Site of action of Parentral Anticoagulants

I. Indirect thrombin inhibitors (Heparin – LMWHs)

Heparin

Chemistry

- Sulfated mucopolysaccharide with high MW.
- Highly acidic with electronegative charge.

Pharmacological Actions

1. Anticoagulant action: (effective both *in vitro* and *in vivo*)

   Mechanism: combines with antithrombin (natural anticoagulant factor) forming heparin-antithrombin complex which accelerates the inhibitory effect of antithrombin on activated clotting factors specially:

   - Factor IIa (Thrombin) - factor IXa - factor Xa.
2. Slight vasodilator effect → canalization of thrombus.
3. Plasma-clearing effect by stimulating lipoprotein lipase enzyme.

Pharmacokinetics

- Immediate onset of action after IV injection and short duration (4-6 h).
- 80 % hepatic metabolism, 20 % excreted renally, unchanged.
- Does not cross placenta & is not secreted in milk (high MW) → can be used during lactation or pregnancy.

Routes of Administration & Doses

- **IV bolus** (5,000 IU), followed by **IV infusion** (1,000 IU/h); guided by aPTT).
- SC: 5,000 IU (low dose of heparin) for prophylaxis, 2 hours preoperative and every 12 hours postoperative for 5-7 days.

Heparin should not be given by IMI as hematoma can occur.

Control of Therapy

- **aPTT** (activated partial thromboplastin time) should be kept as close as possible to twice normal value (normal value 30-35 seconds).

Adverse Effects[1]

1. Hemorrhage ttt: protamine sulfate (antidote).
2. Hair loss (alopecia).
3. Hematoma if given by IMI.
4. Hypersensitivity.
5. Hyperkalemia (monitor K level if heparin is given for more than 7 days)[2].
6. Osteoporosis (on long term use, specially in pregnancy).
7. **Thrombocytopenia** (regular platelet count is required)
    a) Early: mild due to direct effect on platelets.
    b) Late: severe due to immunoglobulin-induced platelet aggregation.

ttt: replace heparin by direct thrombin inhibitors or fondaparinux

---

[1] Heparin may induce thrombosis due to depletion of antithrombin

[2] Hyperkalemia (2^{ry} to aldosterone deficiency) may result due to inhibition of an enzyme necessary for aldosterone synthesis by heparin.

Low-Molecular-Weight Heparins (LMWHs)

(Dalteparin - Enoxaparin -Tinzaparin)

- They are fractions of the standard heparin (unfractionated heparin) thus they have a low molecular weight.
- They are mostly given subcutaneously.

Mechanism of Action

- They bind to antithrombin increasing its inhibitory effect on factor X_a and to a lesser extent on thrombin (Factor II_a).

Advantages of LMWHs

1. Equal efficacy to unfractionated heparin.
2. Greater bioavailability from sc sites.
3. Long $t_{1/2}$ → given subcutaneously once or twice/day.
4. Less thrombocytopenia & osteoporosis.
5. Less risk of bleeding.

II. Indirect selective inhibitor of factor Xa: **Fondaparinux**

- Synthetic pentasacharide molecule, derivative of heparin.
- Binds to antithrombin with high specificity →efficient inactivation of factor Xa.
- Long $t_{1/2}$ → given once daily sc.
- Low risk of heparin - induced thrombocytopenia.
- Used in venous thromboembolism. & heparin - induced thrombocytopenia.
- Bleeding is its major side effect: not antagonized by protamine sulfate.
- Requires less monitoring than heparin (due to predictable pharmacokinetics).

Protamine sulfate

- Highly basic with low MW carrying electropositive charge.
- Neutralizes heparin (each 1 mg neutralizes ≈ 100 IU heparin).
- Partially antagonizes LMWHs but does not antagonize fondaparinux.
- Has a slight anticoagulant effect → avoid overdose.

III. Parentral Direct Thrombin Inhibitors

- Directly bind to thrombin independent of antithrombin → more inhibition of fibrin-bound thrombin.
- Given intravenously.
- Bleeding is its major side effect.

Argatroban

- Preferred in heparin-induced thrombocytopenia in patients with renal insufficiency (cleared hepatically not renally).
- Used in coronary angioplasty in patients with heparin-induced thrombocytopenia.

Bivalirudin [3]

- Used in coronary angioplasty
- Also inhibits platelet activation.

---

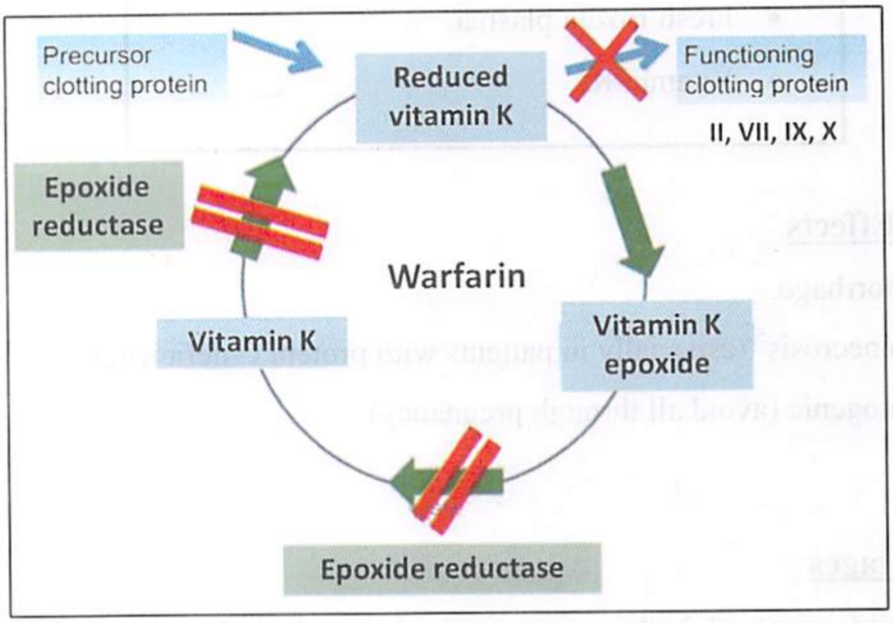
[3] **Bivalirudin**: hirudin analogue.

B. Oral Anticoagulants

I. Warfarin

Mechanism of Anticoagulant Action (effective only *in vivo*)

- Inhibition of vitamin K epoxide reductase enzyme → prevention of reactivation of vitamin K → interference with hepatic synthesis of vitamin K-dependent clotting factors (II, VII, IX, X).


Precursor clotting protein
Reduced vitamin K
Functioning clotting protein
II, VII, IX, X
Epoxide reductase
Warfarin
Vitamin K
Vitamin K epoxide
Epoxide reductase

Pharmacokinetics

- Well absorbed after oral administration(100% bioavailability).
- More than 99 % bound to plasma proteins.
- Metabolized by liver & excreted by kidney.
- Delayed onset with long duration of action (up to 6 days).
- Crosses placenta.
- Secreted in milk (negligible amounts → safe during lactation).

Dosage of Warfarin

- **Loading dose:** 5- 10 mg/day (followed by maintenance dose).
- **Maintenance dose**: 5-7 mg/day (according to INR).

Control of Therapy

- **PT** (Prothrombin Time):

  Should be kept as close as possible to twice normal value (12 s).

- **INR** (International Normalized Ratio)[4]:

  Should be kept at 2-3.

Antidotes

- Fresh frozen plasma.
- Vitamin K_1.

Adverse Effects

1. Hemorrhage.
2. Skin necrosis[5] (especially in patients with protein C deficiency).
3. Teratogenic (avoid all through pregnancy).

Disadvantages

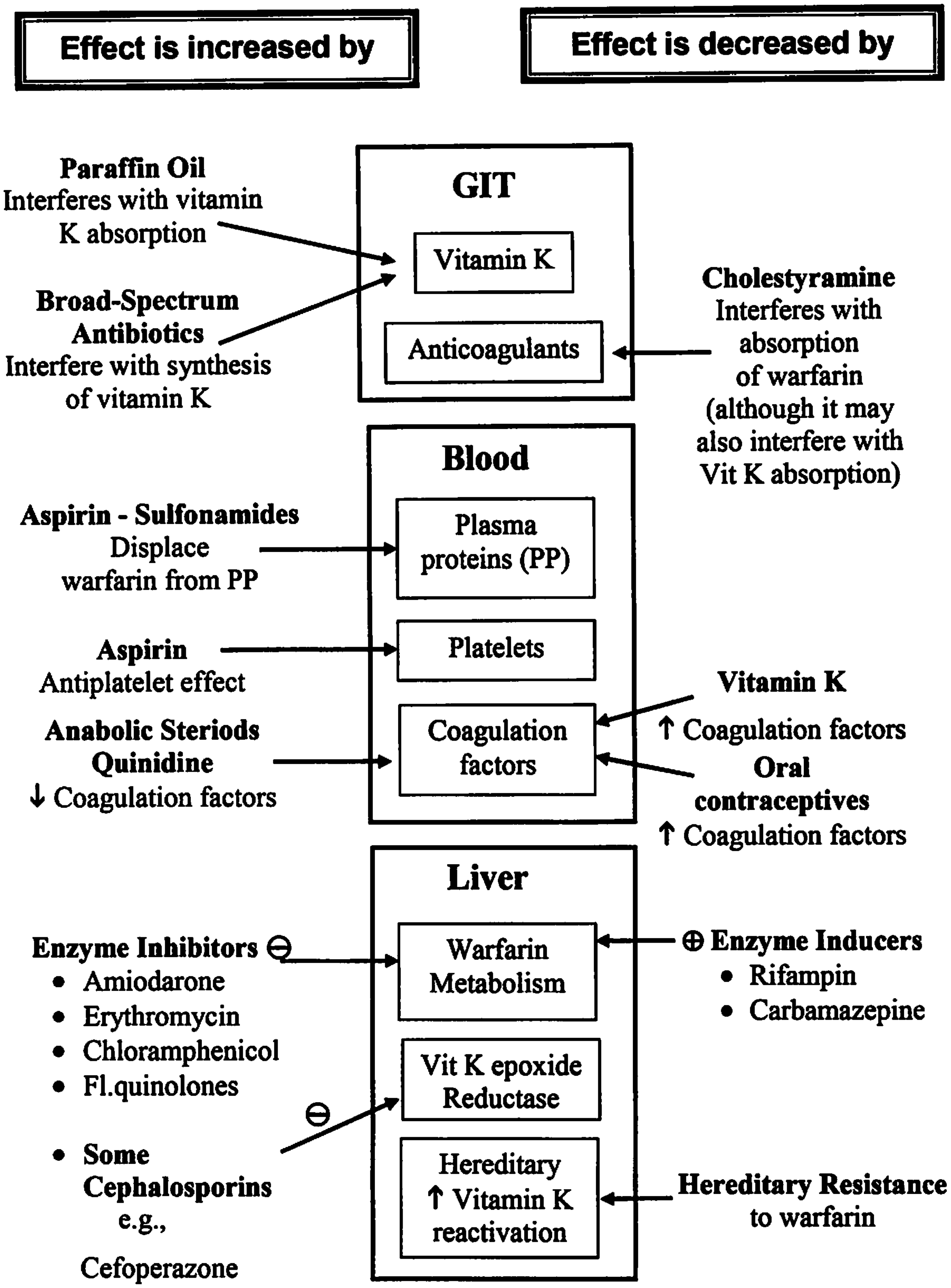
- Delayed onset (2-3 days are required for depletion of already formed coagulation factors) → requires overlapping therapy with heparin (see anticoagulation protocol).
- Narrow therapeutic index
- Requires routine monitoring of coagulation.
- Drug interactions.

---

[4] INR is the ratio of the prothrombin time in the patient to that in a normal non anticoagulated person. Designed to avoid variations between laboratories.

[5] It is due to inhibitory effects of warfarin on synthesis of protein C.The latter is a natural anticoagulant whose level drops at a rate faster than that of the clotting factors → transient hypercoagulation → venular thrombosis → skin necrosis.

Drug Interactions with Warfarin
Requiring Dose Adjustment


Effect is increased by
Effect is decreased by
Paraffin Oil
Interferes with vitamin K absorption
Broad-Spectrum Antibiotics
Interfere with synthesis of vitamin K
GIT
Vitamin K
Anticoagulants
Cholestyramine
Interferes with absorption of warfarin (although it may also interfere with Vit K absorption)
Blood
Aspirin - Sulfonamides
Displace warfarin from PP
Plasma proteins (PP)
Aspirin
Antiplatelet effect
Platelets
Anabolic Steriods
Quinidine
↓ Coagulation factors
Coagulation factors
Vitamin K
↑ Coagulation factors
Oral contraceptives
↑ Coagulation factors
Liver
Enzyme Inhibitors ⊖
• Amiodarone
• Erythromycin
• Chloramphenicol
• Fl.quinolones
Warfarin Metabolism
⊕ Enzyme Inducers
• Rifampin
• Carbamazepine
⊖
Vit K epoxide Reductase
• Some Cephalosporins e.g.,
Cefoperazone
Hereditary ↑ Vitamin K reactivation
Hereditary Resistance to warfarin

II. Newer Oral Anticoagulants (NOAC)

Rivaroxiban – Apixaban - Dabigatran -

Advantages over warfarin

1. More rapid onset and offset.
2. No monitoring is required with less risk of bleeding.
3. Less drug interactions with CYP450 interacting drugs.

Comparison of Oral Anticoagulants

	Warfarin	**Rivaroxaban**	**Dabigatran**
Mechanism	• ↓ Hepatic synthesis of clotting factors (II - VII - IX - X).	• Direct competitive reversible inhibitor of factor **Xa**	• Direct competitive reversible inhibitor of **Thrombin**
Onset	• 36-72 hours	• Within 30 min	• Within 30 min
Duration	• Up to 6 days	• 24 hours	• 24-36 hours
Monitoring	• INR	• No	• No
Antidote	• Vitamin K	• NONE	• Idarucizumab
Interactions	• Significant	• < warfarin	• < warfarin
Renal impairment	• No dose adjustment.	• Dose adjustment • Avoid if creatinine clearance <15ml/min	• Dose adjustment • Avoid if creatinine clearance <15ml/min
Pregnancy	**Teratogenic**	• Unknown	• Unknown

N.B.:

- **Apixaban** is similar to rivaroxaban with less risk of bleeding.
- Dabigatran is a prodrug with very low bioavailability[6]. Absorption depends on acid environment → decreased by proton pump inhibitors.
- Food increases bioavailability of rivaroxaban.

---

[6] Bioavailability: dabigatran: 6.5%, rivaroxaban: 80%, warfarin: 100%.
Dose: rivaroxaban 10-20mg once /day, dabigatran 150mg twice/day, if creatinine clearance > 30ml /min.

Reversal of new oral anticoagulants action in toxicity

1. Activated charcoal →↓absorption (if given within few hours of ingestion).
2. Prothrombin complex concentrate (PCC): reverses rivaroxaban effect.
3. Dialysis for dabigatran; idarucizumab (antidote, recently approved by FDA).

Indications [1](limits propagation & prevents formation of new thrombi)

1. **Prophylaxis of deep venous thrombosis/pulmonary embolism** after knee or hip surgery (Heparin, LMWH, fondaparinaux, warfarin, apixaban and rivaroxaban. Dabigatran used following hip surgery only).
2. **Treatment of deep venous thrombosis/pulmonary embolism** (heparin followed by warfarin, apixaban, rivaroxaban can be used as a single-drug approach, whereas dabigatran and edoxaban are preceeded with LMWH).
3. Stroke prevention in AF cases (warfarin, NOACs used in non-valvular AF).
4. Rheumatic valve disease or mechanical heart valves (Warfarin)
5. Chronic coronary or peripheral artery diseases (Rivaroxaban plus aspirin)
6. Arterial thrombosis: coronary, cerebral; Acute coronary syndrome (Heparin)
7. Cardiac & vascular surgery (heparin) - Hemodialysis (heparin).

Contraindications of Anticoagulants

I. Increased risk of bleeding

Hemophilia- purpura- head injuries- intracranial hemorrhage.

Severe hypertension- threatenend abortion - active peptic ulcer - active TB.

II. Allergy

Protocol for anticoagulation

- Heparin (initially), followed by concomitant administration of oral anticoagulants for 2-3 days before stopping heparin (guided by INR).
- Rivaroxaban is approved as initial oral treatment of deep vein thrombosis (DVT).

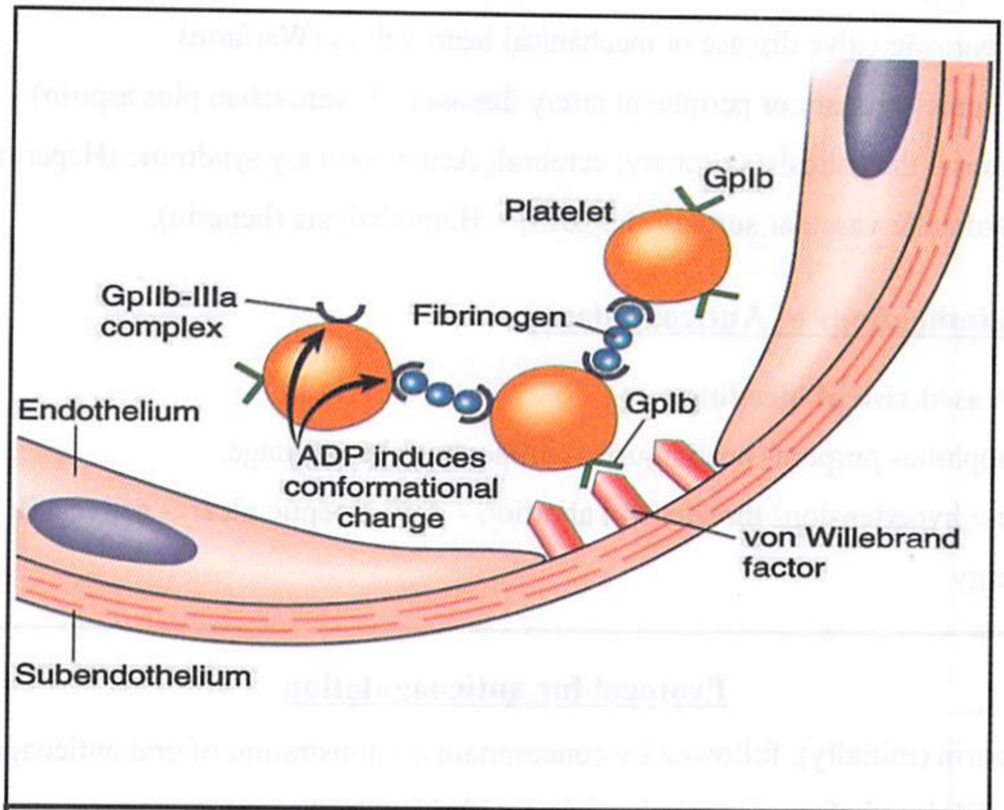
---

[1] The recommended dosage of rivaroxaban is 15mg twice daily for the first 21 days followed by 20mg once daily for continued treatment and prevention of recurrence.

ANTIPLATELET DRUGS

Platelet Aggregation

- Damage of vessel wall → exposure of collagen in subendothelium → platelet adhesion (enhanced by factor VIII and von Willebrand factor) followed by activation→ release reaction (ADP, fibrinogen TXA_2, etc….).
- ADP binds to its receptor on platelets → exposure of glycoprotein GP IIb/IIIa receptor on platelet membrane.
- Fibrinogen binds to the GP IIb/IIIa receptor linking adjacent platelets → aggregation.


GpIb
Platelet
GpIIb-IIIa complex
Fibrinogen
Endothelium
GpIb
ADP induces conformational change
von Willebrand factor
Subendothelium

Steps of Platelet Aggregation.

Classification of antiplatelets according to mechanism of Action

I. Drugs Acting on Platelet COX Enzyme

Acetylsalicylic acid (Aspirin)

- Prototype antithrombotic
- Low-dose aspirin (75 - 325 mg/day oral): inhibits platelet thromboxane A_2 synthesis by inhibiting (irreversible acetylation) of COX -1 enzyme[8].
- Aspirin is the main antiplatelet drug used. Clopidogrel or dypiridamole may be combined to it or given to patients intolerant to it.

II. Drugs Increasing cAMP

1. PGI_2 analogue (epoprostenol)

- Stimulates adenyl cyclase→ ↑cAMP.
- Potent antiplatelet & vasodilator.
- Very short duration (minutes)→ given by IVI.

2. Dipyridamole & **Cilostazol** (oral)

- Inhibit phospho-diesterase →↓ cAMP breakdown.
- Vasodilator & antiplatelet.
- Dipyridamole is a weak antiplatelet →combined with warfarin or aspirin.
- Dipyridamole: prefered to aspirin for combination with warfarin (less bleeding).

III. Drugs acting on platelet ADP & fibrinogen Receptors

1. Drugs inhibiting ADP receptors →inhibit expression of fibrinogen receptors

- Ticlopidine- clopidogrel - prasugrel – ticagrelor (oral)

2. Drugs blocking GP IIb/IIIa Fibrinogen Receptor

- Tirofiban , eptifibatide , abciximab (mono-clonal antibody)
  (All are given IVI; short term therapy).

---

[8] Low dose aspirin is selective on platelets because platelets are exposed to aspirin in the portal circulation before its acetylation by first pass metabolism. Since platelets are nonnucleated,they cannot resynthesize new COX. Thus antiplatelet effect of aspirin remains for 7-10 days (life span of platelet) after which new platelets are formed with new COX. Vascular endothelial cells are nucleated thus can regenerate COX. Thus prostacyclin synthesis recovers rapidly.

Therapeutic uses of antiplatelet drugs (mainly in arterial thrombosis)

1. High risk of myocardial infarction (AMI): e.g., previous attack or angina (**aspirin**).
2. Acute coronary syndrome (**aspirin +clopidogrel**[9] **or abciximab**).
3. Coronary bypasses grafting, angioplasty & stent insertion (**aspirin plus clopidogrel** or **abciximab**).
4. Prosthetic heart valves: ↓thrombo-embolism (**dipyridamole plus warfarin**).
5. Transient ischemic attacks- thrombotic stroke (**dipyridamole plus aspirin**).
6. Hemodialysis- cardiopulmonary bypass- pulmonary hypertension (**epoprostenol**).
7. Intermittent claudication (**cilostazol**).

N.B.: Antiplatelets may be given in atrial fibrillation if anticoagulants are CI.

Side effects of antiplatelet drugs:

1. Aspirin: oral once /day

1. GIT: gastric irritation, bleeding ulcers.
2. ↑ Risk of bleeding.
3. Hypersensitivity
4. Hyperuricemia.

2. Ticlopidine: (oral) GIT irritation -neutropenia

3. Clopidogrel: oral once /day (preferred to ticlopidine; less risk of neutropenia)

- Bleeding- rash - Gastric irritation, diarrhea.
- Clopidogrel is a prodrug→ avoid with omeprazole as it inhibits its activation in liver.

4. Prasugrel: (oral)

- Increased risk of bleeding (CI: in patients with history of TIA or stroke)

5. Ticagrelor: bleeding - shortness of breath

6. Dipyridamole (oral): Steal phenomena –dizziness- headache- GIT disturbance.

7. Epoprostenol (IVI): Flushing, headache, hypotension.

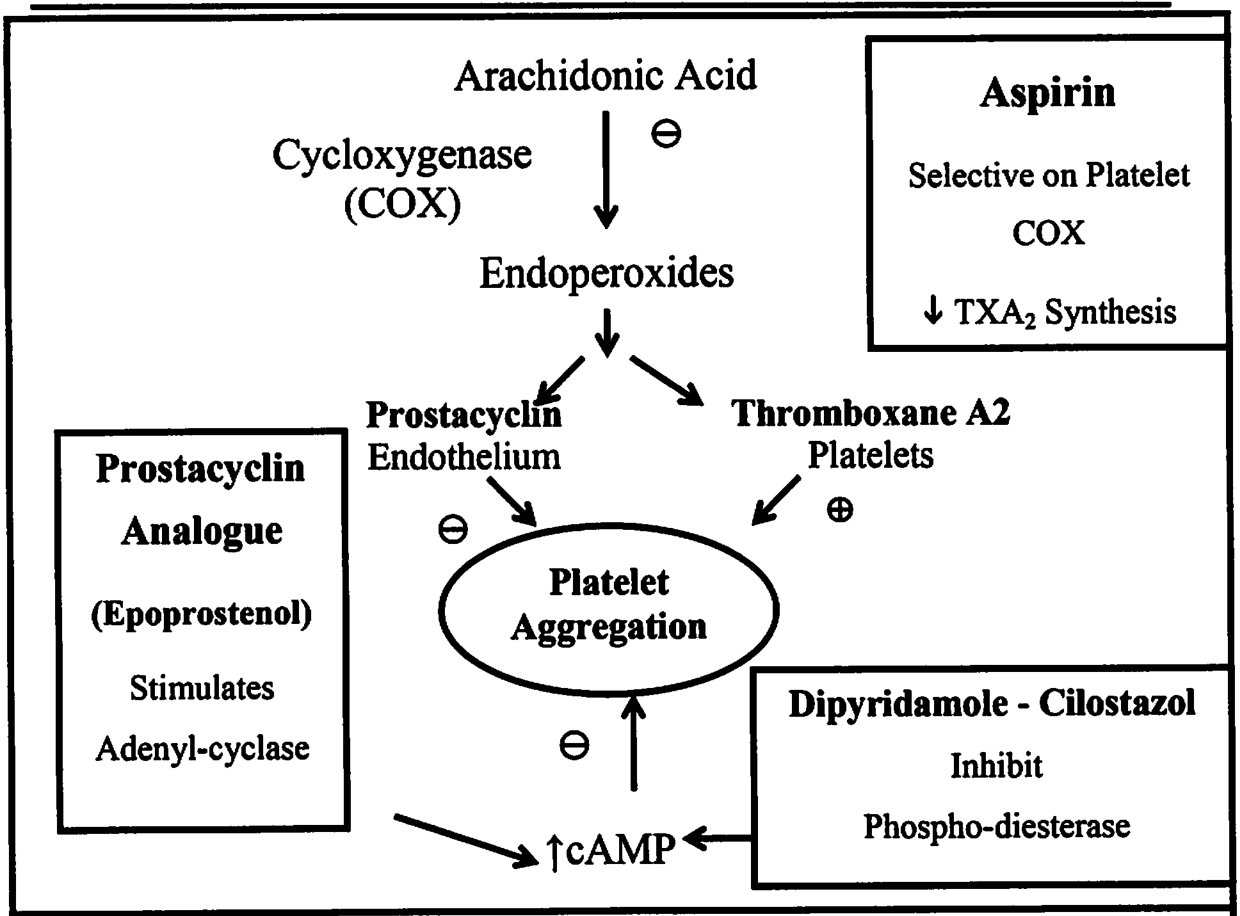
8. Abciximab (IVI): bleeding, thrombocytopenia, arrhythmia.

9. Cilostazol (oral):

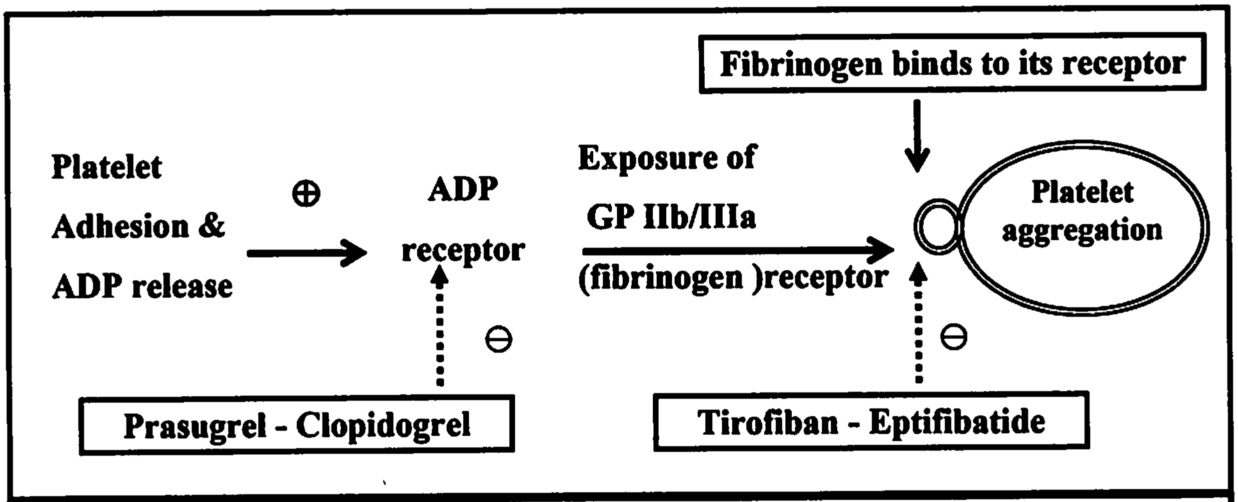
- Headache, dizziness - GIT upset: nausea, dyspepsia, diarrhea
- Tachycardia, palpitations, peripheral edema.

---

[9] Ticlopidine, prasugrel & ticagrelor are also used in acute coronary syndrome.


Arachidonic Acid
Cycloxygenase (COX)
⊖
Endoperoxides
Aspirin
Selective on Platelet COX
↓ TXA_2 Synthesis
Prostacyclin
Endothelium
Thromboxane A2
Platelets
⊖
⊕
Prostacyclin Analogue
(Epoprostenol)
Stimulates Adenyl-cyclase
Platelet Aggregation
⊖
Dipyridamole - Cilostazol
Inhibit Phospho-diesterase
↑cAMP

Antiplatelet Drugs Acting on Platelet COX enzyme & cAMP.


Fibrinogen binds to its receptor
Platelet Adhesion & ADP release
⊕
ADP receptor
Exposure of GP IIb/IIIa (fibrinogen)receptor
Platelet aggregation
⊖
⊖
Prasugrel - Clopidogrel
Tirofiban - Eptifibatide

Site of Action of Antiplatelets on Platelet ADP & Fibrinogen Receptors

FIBRINOLYTICS (THROMBOLYTICS)

- Drugs that cause lysis of thrombus. They are given intravenously.

Mechanism of Action

- Fibrinolytics are plasminogen activators. They activate plasminogen to plasmin which causes degradation of fibrin:

Plasminogen (natural plasma glycoprotein) $\xrightarrow[\text{activators}]{\text{Plasminogen}}$ **plasmin** → **dissolves fibrin (clot)**

N.B.:

- Plasmin digests not only fibrin but also fibrinogen and factors V & VIII. So bleeding may occur if excess plasmin circulates in plasma.

The ideal fibrinolytic is that which activates plasminogen bound to fibrin (fibrin-specific) without activating free plasminogen in plasma.

So its effect is localized to clot → ↓ risk of bleeding.

Indications of Fibrinolytics

1. Acute myocardial infarction (most effective if given early within 6 hours).
2. Pulmonary embolism.
3. Deep venous thrombosis.
4. Thrombotic stroke (tPA within 3 hours).
5. Obstructed arterio-venous shunt & occlusion of intravascular catheter.

Fibrinolytic therapy should be started as soon as possible after the onset of thrombosis or embolism (since they become resistant to lysis as they age).

Classification of Fibrinolytics[10]

Fibrin-Nonspecific
(1st generation)

A. Streptokinase (SK)
B. Urokinase (UK)

- **Non clot-selective**: activate both circulating & clot (fibrin)-bound plasminogen:

A. **SK:** acts indirectly forming a complex with plasminogen which then activates free plasminogen
Advantage: (cheapest & most widely used).

B. **UK:** directly activates plasminogen
Advantage: (non antigenic).

Disadvantages

- ↑ bleeding risk (non clot-selective)
- Antigenic (SK).
- Given as intravenous infusion→loading dose followed by maintenance dose.

Fibrin-specific
(2nd generation)

Tissue Plasminogen Activators (tPA)

Alteplase – Tenecteplase

Reteplase

- **Clot-selective**: greater affinity for activating clot (fibrin)-bound plasminogen than circulating plasminogen.

Advantages

- ↓ Bleeding risk (clot-selective).
- Nonantigenic.
- Tenecteplase is given as a single IV bolus dose (longer $t_{1/2}$).
- Reteplase: longer $t_{1/2}$

---

[10] **Source**: streptokinase: cultures of β-hemolytic streptococci, urokinase: cultures of human renal cells & urine, alteplase (human tPA): recombinant DNA tech. & tenecteplase: mutant of tPA.

Adverse Effects

1. Bleeding (more with fibrin-nonspecific agents → treated by stopping infusion, fresh blood & antifibrinolytics).
2. Antigenicity (fever, allergy & hypotension) with streptokinase[11] → start therapy with a large loading dose to neutralize antibodies).
3. Recurrence of thrombosis.

Contraindications

1. Recent surgery.
2. Gastrointestinal bleeding.
3. Hypertension.
4. Cancer.
5. Pregnancy.
6. Children & old age.

Fibrinolytics should be followed by anticoagulants & antiplatelets because as the clot dissolves local thrombin increases, → ↑ platelet aggregation & thrombosis.

---

[11] Due to antibody formation following previous streptococcal infection.

DRUGS USED IN BLEEDING DISORDERS

I. VITAMIN K

- Fat-soluble vitamin essential for hepatic synthesis of factors II, VII, IX and X.
- Deficiency of vitamin K leads to spontaneous hemorrhage.

Types of Vitamin K

1. Natural

- Bile salts essential for absorption.
  - K_1 in plants (IM - oral).
  - K_2 synthesized by GIT bacteria.

2. Synthetic

- Water-soluble → no need for bile.
  - K_3
  - K_4

Indications of Vitamin K

1. Overdose of anticoagulants & salicylates.
2. Hemorrhagic diseases in newborn.
3. Vitamin K deficiency (in obstructive jaundice or malabsorption syndrome).

Adverse Effects

- Rapid IV injection results in:
  1. Dyspnea.
  2. Chest pain.
  3. Flushing.

II. FIBRINOLYTIC INHIBITORS (ANTIPLASMIN)

1. Aminocaproic Acid

- Competitive inhibitor of plasminogen activators.

Uses

1. Bleeding due to fibrinolytics.
2. Adjunct therapy in hemophilia.
3. Bleeding states resulting from damage of tissues rich in plasminogen activators (e.g. after prostatic surgery, tonsillectomy).

Adverse Effects

- Hypotension.
- Abdominal discomfort.
- Intravascular thrombosis.

2. Tranexamic Acid

- Analog of aminocaproic acid that is more potent with fewer side effects.

III. Plasma Fractions

- Given when there is deficiency of one of the coagulation factors, e.g.:
    - Factor VIII given in hemophilia.
    - Factor IX.
    - Fibrinogen.

Cryoprecipitate

Plasma protein rich in factor VIII, von Willebrand factor & firbinogen.

DRUG THERAPY OF ANEMIAS

- Normal erythropoiesis requires certain exogenous substances (iron, folic acid & vitamin B_{12}) & some endogenous factors (intrinsic factor, erythropoietin & colony stimulating factors).

DRUG THERAPY OF IRON-DEFICIENCY ANEMIA

(Microcytic Hypochromic Anemia)

IRON

Iron Absorption

- Takes place in upper part of small intestine (acid medium ↑ solubility).
- Ferrous iron is more readily absorbed than ferric.

Factors Enhancing Iron Absorption

1. Infancy, adolescence and in iron-deficiency anemia (↑ demand)
2. Ascrobic acid, HCl & succinic acid → ↑ absorption (ferric → ferrous).

Factors Reducing Iron Absorption[12]

1. Gastric resection and malabsorption syndrome.
2. Desferrioxamine (chelates iron).
3. Antacids.
4. Tannic acid (precipitates iron).
5. Tetracyclines & iron bind together → ↓ absorption of both.
6. Calcium in dairy foods → ↓ iron absorption.
7. Phosphates, oxalates and phytates (form insoluble iron complexes).

---

[12] Foods that decrease non-heme iron absorption have little effect on absorption of heme iron. Heme iron is found in meat, non-heme iron is found in plants and in iron supplements.

Indications of Iron Therapy:

1- Prophylactic, to prevent development of iron-deficiency anemia (IDA):
30-60 mg/day elemental iron[13].

2- Treatment of IDA:
200-400 mg/d elemental iron [14].

Iron-Deficiency Anemia due to:

1. ↑ **Demand:** premature infants, children during rapid growth, pregnant and lactating women.
2. ↓ **Absorbtion:** after gastrectomy & in malabsorption syndrome.
3. **Chronic blood loss**, e.g., occult GIT bleeding, heavy menstrual bleeding, during hemodialysis, ankylostomiasis.
4. ↑ **in blood formation:** during treatment of severe pernicious anemia with vitamin B12 (depletion of iron stores), during treatment with erythropoietin (formation of RBCs at a high rate).

Iron Therapy (Oral - IV - IM)

I. Oral Iron Therapy

Ferrous salts are usually used as ferrous iron is efficiently absorbed.

- Effective & cheap (treatment of choice).
- Oral preparations include ferrous sulfate, gluconate and fumarate.
- Different Fe salts provide different amounts of elemental Fe (range from 12-33%)
- **New agents**: polysaccharide-iron complex 150 mg, carbonyl iron 150 mg contain 100% elemental iron.
- Heme iron polypeptide: More expensive than above agents.
- Given after meals to ↓ GIT disturbances (carry risk of ↓absorbed portion).
- Continue iron till Hb is normal & for an extra 2-3 months to replenish stores.

---

[13] Elemental iron is the total amount of iron in the supplement available for absorption.

[14] In Fe deficient individuals, about 50-100 mg of Fe can be incorporated into hemoglobin daily, and about 25% of oral Fe given can be absorbed.

Adverse Effects of Oral Iron Therapy

1. GIT disturbances: nausea, epigastric pain, constipation (given after meals - start with small dose then gradually increase).
2. Black stools (mask diagnosis of GI bleeding).
3. Black staining of teeth (iron sulfide in mouth).

II. Parenteral Iron Therapy

Indications (= **Causes of failure of oral iron therapy**)

1. Noncompliance to oral therapy (severe GIT disturbance or ulceration).
2. Malabsorption syndrome causes failure of iron absorption.
3. Severe anemia, e.g. in malignancy.

Calculation of Parentral Iron

(There are many formulae to determine parenteral iron required to correct anemia & replenish stores).

e.g.

Total iron deficit (mg) = Body weight [kg] x (Target Hb – Actual Hb) [g/l] x 2.4 + 500 [mg] (for iron stores)

Parenteral Iron Preparations

A. Iron dextran

B. Iron sucrose complex & Iron sodium gluconate complex.

C. **Newer preparations:** Ferric carboxymaltose, Ferumoxytol

- Given by **deep IMI** or by **IV infusion**[15] (as a total dose infusion, **TDI**).

Advantages of TDI

1) Avoids non-compliance of the patient.
2) Avoids unpleasant effects of IMI.
3) Allows delivery of the entire dose of iron necessary to correct iron deficiency at one time.

Adverse Reactions of parenteral iron therapy

- **IM:** local pain - tissue staining.
- **IV:** headache, fever, urticaria, lymphadenopathy & anaphylactic shock (with Fe dextran, start with a small test dose).

Iron Toxicity

Acute Iron Toxicity (more in children)

- Abdominal pain, vomiting, bloody diarrhea, dyspnea followed by metabolic acidosis, cardiovascular collapse, convulsions, coma & death.

Treatment (urgent and immediate)

1. Raw egg or milk → bind & precipitate iron as albuminate or caseinate until a chelating agent is available.
2. **Desferrioxamine:**
    - 1-2 g IM or IV → chelates iron promoting its excretion in urine.
    - 5 g in 100 ml water swallowed or by stomach tube (after gastric lavage with bicarbonate solution[16].
3. IV infusion of saline, dextrose or bicarbonate → correct water & electrolyte disturbance.

---

[15] Start with a small test dose.

[16] Bicarbonate forms insoluble iron salts.

Chronic Iron Toxicity

It occurs in:

1. Patients receiving many red cell transfusions.
2. Patients with hemochromatosis; an inherited disorder characterized by ↑ Fe absorption → hemosiderosis (Fe^{3+} preciptation in vital organs).

Management

1. Venesection [17] (if no anemia) → repeated weekly.
2. Desferrioxamine IM or SC.
3. Large intake of tea → tannins binds iron.

Anemia of chronic disease:

- It is a functional iron deficiency anemia.
- Occurs when there is infection and inflammation with release of cytokines that stimulate the release of hepcidin from the liver.
- High levels of hepcidin prevent absorption & release of iron from its storage sites (sequestrated anemia).
- To be differentiated from iron deficiency anemia, there is normal or high serum ferritin.
- Not treated with iron but its treatment is to treat infection & inflammation.

---

[17] A single venesection of 500 ml blood removes 200 mg iron.

DRUG THERAPY OF MEGALOBLASTIC ANEMIA

(Vitamin B_{12} and Folic Acid Deficiency)

I. Vitamin B_{12}

- Cobalt-containing compound synthesized by bacterial flora in colon.
- Called extrinsic factor to differentiate it from an intrinsic factor (a glycoprotein formed by parietal cells, necessary for vitamin B_{12} absorption).

Functions of Vitamin B_{12}: It is essential for:

1. Cell growth and replication (DNA synthesis).
2. Maintenance of normal myelin sheath, erythropoiesis and cell maturation.
3. Normal metabolic functions of folate.

If vitamin B_{12} absorption is stopped, it takes 5 years for megaloblastic anemia to develop since its daily requirement is 2 μg & body store is relatively high.

Pernicious Anemia

- It is a severe form of megaloblastic anemia due to deficiency of intrinsic factor (congenital, after gastrectomy). The disease is characterized by:
  1. Megaloblastic anemia (large red cells highly susceptible to destruction).
  2. Subacute combined degeneration of brain, spinal cord & peripheral nerves.
  3. Atrophic gastritis.

Preparations of Vitamin B_{12}

A. Cyanocobalamin

B. Hydroxycobalamin (preparation of choice):

1. More slowly absorbed.
2. More bound to plasma proteins.
3. Slowly excreted.
4. More sustained rise in serum cobalamin.

Therapeutic uses of Vitamin B_{12}

A. Megaloblatic Anemia

1. **Pernicious anemia**: vitamin B_{12} is given for life by IMI.
    - Initial therapy: 1,000 µg/day for 1-2 week to replenish stores. Then 1,000 µg/week till normal blood count.
    - Maintenance therapy: 1,000 µg/month for life.
2. **Megaloblastic anemia** due to diphylobothriasis.
    - It is treated by vitamin B_{12} and praziquantel.
3. **Drug-induced megaloblastic anemia:**
    - Neomycin, colchicine and antiepileptics reduce absorption of B_{12}.

B. Neurological Conditions

- Peripheral neuritis in diabetes & retrobulbar neuritis in heavy smokers.

II. Folic Acid

(Pteroylglutamic Acid)

- **Source:** liver, yeast and green vegetables.
- Essential for DNA synthesis.
- Vitamin B_{12} is essential for activation of folic acid. So vitamin B_{12} deficiency is often associated with folic-acid-deficiency anemia.
- No neurological abnormalities are associated with folate deficiency.

Folate deficiency develops more rapidly than vitamin B_{12} deficiency since daily requirement is high and body store of folate is low.

Causes of Folic Acid Deficiency

1. Inadequate dietary supply or increased demand (e.g. pregnancy, lactation).
2. Diseases in small intestine.
3. Alcoholism.
4. **Drug-induced folic acid deficiency:**
    a. Phenytoin, phenobarbitone & oral contraceptives (interfere with folate absorption).
    b. Methotrexate, trimethoprim & pyrimethamine (inhibit dihydrofolate reductase enzyme) **[Treated by folinic acid].**

Therapeutic uses of folic Acid

1. Nutritional megaloblastic anemia.
2. Malabsorption syndrome.
3. In alcoholics and pregnant women.
4. Patients with liver disease & with hemolytic anemia.
5. With anticonvulsant drugs.
6. Patients on dialysis (as folic acid is removed each time).

DRUG-INDUCED BLOOD DISORDERS

A. Hemolytic Anemia (destruction of RBCs)

1. In G6PD-deficient subjects

1. Antimalarial drugs.
2. Aspirin.
3. Sulfonamides.
4. Quinine and quinidine.

2. As a Hypersensitivity Reaction

1. Penicillin
2. Sulfonamides.

3. Autoimmune Hemolytic Anemia: methyldopa.

B. Thrombocytopenia

- Heparin - rifampin - indomethacin - quinine - quinidine.
- **Treatment:** stop the drug - platelet transfusion - corticosteroids.

C. Bone Marrow Depression (aplastic Anemia or agranulocytosis)

- Cytotoxic drugs - chloramphenicol - chlorpromazine - thiouracil.

Treatment of agranulocytosis or aplastic anemia

1. Blood transfusion to replace lacking components.
2. Treatment according to cause (if known).
3. Corticosteroids: reduce bleeding due to thrombocytopenia.
4. Broad-spectrum antibiotics, e.g. penicillins to treat infections.
5. Bone marrow transplantation (treatment of choice) followed by immunosuppression with cyclosporin to prevent graft rejection.
6. Erythropoietin.

Erythropoietin (IV or SC)

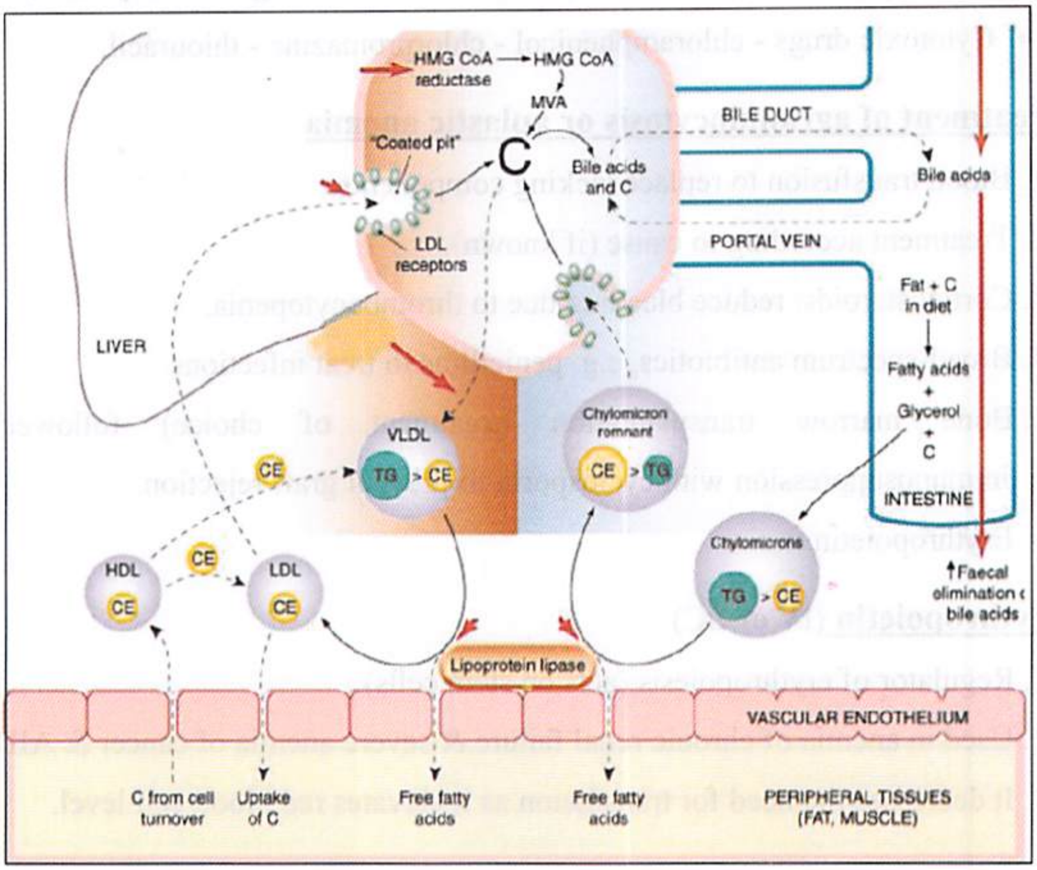
1. Regulator of erythropoiesis (acts on stem cells).
2. Used in anemia of chronic renal failure & severe anemia of cancer & AIDS.
3. It decreases the need for transfusion as it elevates red blood cell level.

DRUG THERAPY OF HYPERLIPIDEMIA

- Hyperlipidemia (hyperlipoproteinemia) is an increase in plasma lipoproteins & is one of the risk factors for ischemic heart disease.
- Cholesterol and TGs are insoluble in blood & therefore carried as lipoproteins.

Types of Lipoproteins

1. **Chylomicrons** (TGs): formed in GIT from dietary TG.
2. **VLDL**: synthesized in liver; formed mainly of TGs (synthesized from FAs derived from lipolysis of TG by intracellular lipase in adipose tissue) & some cholesterol (synthesized from HMG-CoA by HMG-CoA reductase)
3. **IDL** (TGs, cholesterol): derived from VLDL hydrolysis by lipoprotein lipase.
4. **LDL** (cholesterol): derived from hydrolysis of IDL. Plasma LDL cholesterol is uptaken by liver through LDL receptors.
5. **HDL** (protective) → removes cholesterol from tissues to be degraded in liver.

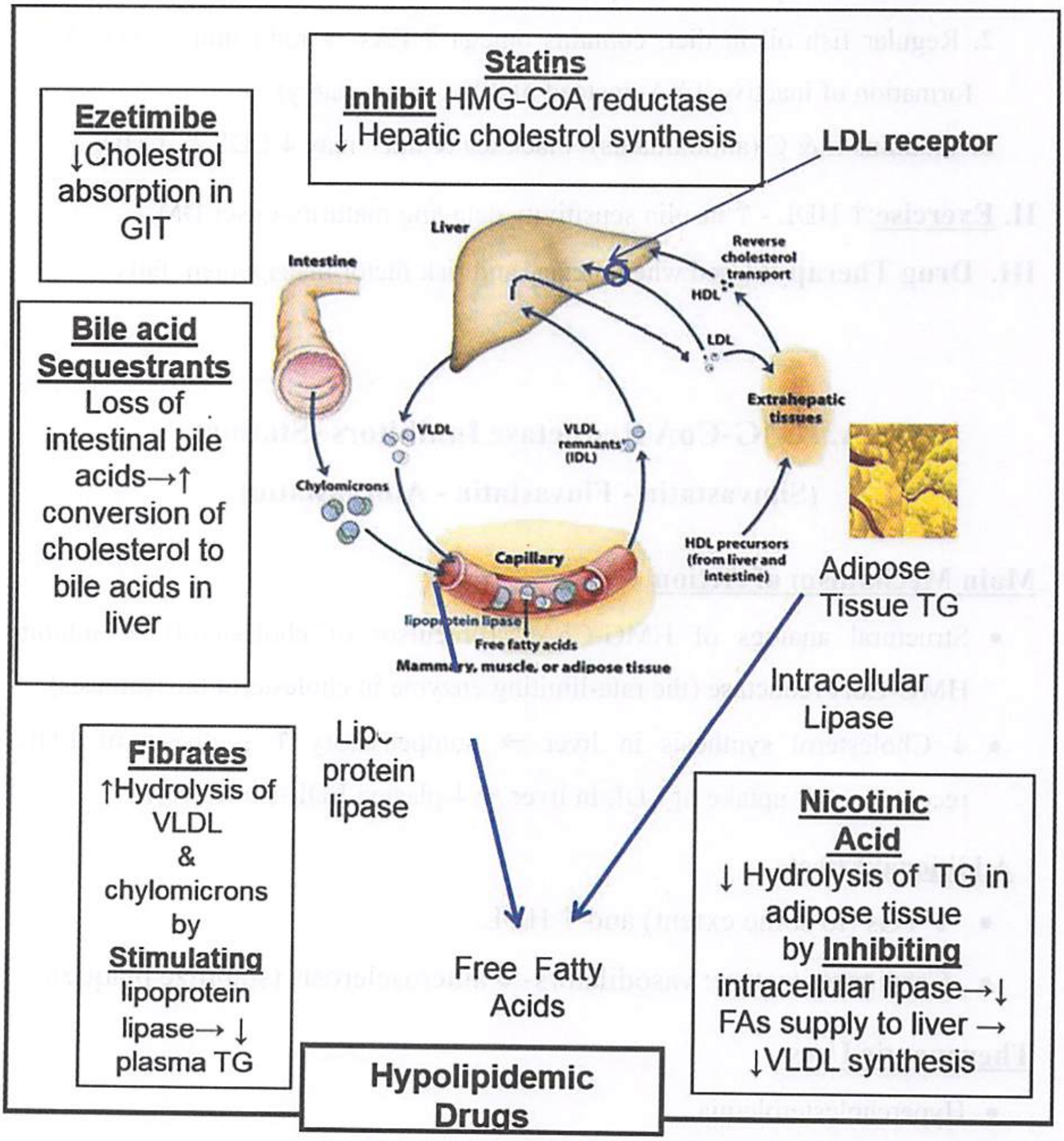

HMG CoA reductase
HMG CoA
MVA
"Coated pit"
C
Bile acids and C
BILE DUCT
Bile acids
PORTAL VEIN
LDL receptors
LIVER
Fat + C in diet
Fatty acids
+
Glycerol
+
C
INTESTINE
VLDL
TG > CE
CE
Chylomicron remnant
CE > TG
Chylomicrons
TG > CE
HDL
CE
LDL
CE
↑Faecal elimination of bile acids
Lipoprotein lipase
VASCULAR ENDOTHELIUM
C from cell turnover
Uptake of C
Free fatty acids
Free fatty acids
PERIPHERAL TISSUES (FAT, MUSCLE)

Etiology of Hyperlipidemias:

1^{ry} (genetic origin): hereditary.

2^{ry} due to:

- **Diseases**: DM, hypothyroidism, nephrotic syndrome, obesity.
- **Drugs**: β blockers, diuretics, progesterone, alcohol.


Liver
Intestine
Reverse cholesterol transport
HDL
LDL
Extrahepatic tissues
VLDL
VLDL remnants (IDL)
Chylomicrons
Capillary
HDL precursors (from liver and intestine)
lipoprotein lipase
Free fatty acids
Mammary, muscle, or adipose tissue

Ezetimibe
↓Cholestrol absorption in GIT

Statins
Inhibit HMG-CoA reductase
↓ Hepatic cholestrol synthesis

LDL receptor

Bile acid Sequestrants
Loss of intestinal bile acids→↑ conversion of cholesterol to bile acids in liver

Adipose Tissue TG

Intracellular Lipase

Lipo protein lipase

Fibrates
↑Hydrolysis of VLDL & chylomicrons by **Stimulating** lipoprotein lipase→ ↓ plasma TG

Nicotinic Acid
↓ Hydrolysis of TG in adipose tissue by **Inhibiting** intracellular lipase→↓ FAs supply to liver → ↓VLDL synthesis

Free Fatty Acids

Hypolipidemic Drugs

Management of Hyperlipidemias

I. Diet

1. Avoid saturated FAs (animal fats). Use unsaturated FAs (plant fats), e.g. olive or sunflower oil: Polyunsaturated FAs → ↑ conversion of free cholesterol (active) to cholesterol ester (inactive) → ↓ hepatic free cholesterol → compensatory ↑ LDL receptors → ↑ uptake of LDL → ↓ plasma LDL.
2. Regular fish oil in diet: contains omega *3* FAs → reduction in TGs & formation of inactive TXA_3 instead of TXA_2 (aggregatory).
3. Vitamins E & C (antioxidants)- black tea & nuts: may ↓ LDL & ↑ HDL.

II. Exercise: ↑ HDL - ↑ insulin sensitivity delaying maturity-onset DM.

III. Drug Therapy: Used when dietary and risk factor management fails.

A. HMG-CoA Reductase Inhibitors (Statins)

(Simvastatin - Fluvastatin - Atorvastatin)

Main Mechanism of Action

- Structural analogs of HMG-CoA[18] (precursor of cholesterol) → inhibit HMG-CoA reductase (the rate-limiting enzyme in cholesterol biosynthesis).
- ↓ Cholesterol synthesis in liver → compensatory ↑ synthesis of LDL receptors → ↑ uptake of LDL in liver → ↓ plasma LDL-cholesterol.

Additional Effects

- ↓ TGs (to some extent) and ↑ HDL.
- Cardiopreotective: vasodilators- ↓ atherosclerosis (stabilize plaque).

Therapeutic Uses

- Hypercholesterolemia.
- Combined hyperlipidemia (↑ cholesterol and TGs).

---

[18] Hydroxy-methylglutaryl-CoA.

Adverse Effects

- Myopathy and muscle damage leading to renal failure in patients with renal dysfunction especially when combined with fibrates or nicotinic acid.
- Increase in serum liver enzymes **(CI in hepatic dysfunction).**
- Cataract.
- GIT disturbances.

B. Bile Acid Sequestrants

(Cholestyramine - Colestipol)

Mechanism

- Anion-exchange resins; bind bile acids in intestine→ prevent absorption.
- Loss of bile acids → ↑ conversion of cholesterol into bile acids in the liver.
- ↓ Conc. of intrahepatic cholesterol → compensatory ↑ LDL receptors → ↑ hepatic uptake of circulating LDL → ↓ serum LDL-cholesterol.

Therapeutic Uses

- Hypercholesterolemia (in addition to statins when response to statins is inadequate or in cases where statins are contraindicated).
- Addition of statins offsets the compensatory ↑ in cholesterol synthesis resulting from ↓ hepatic cholesterol with long term cholestyramine therapy.

Adverse Effects

1. GIT disturbance.
2. ↓ Absorption of digitalis and warfarin (binding).
3. ↓ Absorption of fat-soluble vitamins (due to loss of bile salts in stool).

C. Activators of Lipoprotein Lipase (Fibrates)

(Fenofibrate – Gemfibrozil)

Main Mechanism of Action

- Agonists at PPAR-α receptor subtype → expression of genes responsible for ↑ activity of plasma lipoprotein lipase enzyme → hydrolysis of VLDL and chylomicrons → ↓ serum TGs levels.

Additional Effects

- ↑ Clearance (uptake) of LDL by liver & ↑ HDL.

Therapeutic Uses

Hypertriglyceridemia - combined hyperlipidemia if statins are contraindicated.

Adverse Effects

1. GIT disturbances.
2. Gallstones.
3. Muscle pain & myopathy (patients with renal impairment are at risk).

D. Inhibitors of Lipolysis

Nicotinic Acid

- It was the first and cheapest hypolipidemic drug.
- It ↓ both TGs (VLDL) and cholesterol (LDL) levels.

Mechanism

- Potent inhibitor of lipolysis in adipose tissue → ↓ mobilization of FFAs to liver → ↓ VLDL (after few hours).
- Since LDL is derived from VLDL, ↓ VLDL → ↓ LDL (after few days).
- ↑ HDL.

Therapeutic Uses

- Hyperlipidemia (↑ VLDL, ↑ LDL).
- Severe hypercholesterolemia, combined with fibrate or cholestyramine.

Adverse Effects (limit its use especially after introduction of statins)

- Cutaneous flush (PG-mediated; ↓ by aspirin) & pruritus.
- GIT disturbance.
- Glucose intolerance.
- Gouty arthritis (hyperuricemia).
- Myopathy (rare).

E. Ezetimibe

- Inhibits intestinal cholesterol absorption.
- Used in hypercholesterolemia together with statins & diet regulation.
- **Side effects**: diarrhea - abdominal pain.

Combination Therapy

If no improvement within 6 weeks with a single drug, dose should be ↑. If no improvement after 3 months, change the drug or consider combination therapy:

- Bile acid sequestrants can be **safely combined** with statins or nicotinic acid.
- Nicotinic acid + statins **(cautiously → myopathy)**.
- Fibrates (except fenofibrate) + statins **(contraindicated → myopathy)**.
- Ezetimibe + statins (synergistic effects).

Newer agents for treatment of dyslipidemia[19]

1. **Microsomal triglyceride transfer protein (MTP) inhibitors**: Lomitapide
    - Inhibit MTP (involved in formation of hepatic VLDL & intestinal chylomicrons from TG) → ↓VLDL →↓LDL accumulation in plasma.
    - **Use**: restricted to patients with familial hypercholesterolemia through a restricted program.
    - **Side Effects**: accumulation of TG in liver, ↑ transaminases , steatorrhea.

2. **Anti-sense inhibition of apo B 100 synthesis**: Mipomersen
    - ↓ Level of LDL and Lp(a).
    - SC injection available for familial hypercholesterolemia through a restricted program

3. **Cholesteryl ester transfer protein (CETP) inhibitors[20]**: anacetrapib, evacetrapib
    - ↑ HDL and ↓ LDL.
    - Currently in phase 3 clinical trials.

4. **AMP kinase activation**:
    - ↑ fatty acid oxidation
    - ↑insulin sensitivity
    - Inhibits cholesterol and TG synthesis.

---

[19] Proprotein convertase subtilisin/kexin type 9 (PCSK 9) inhibition: parenterally twice weekly → ↓ LDL, TG, apo B100 and Lp(a). Under investigation because of established role of PCSK 9 in normal neuronal apoptosis and cerebral development.

[20] Torcetrapib was withdrawn from clinical trials as it ↑ cardiovascular events & deaths.

IV. Respiratory Pharmacology

Intended Learning Outcomes (ILOs)

By the end of this chapter, the student should be able to:

- Classify antiasthma drugs into short-term reliever bronchodilators & long-term controller anti-inflammatory drugs.
- Recall the management strategy for asthma according to the guidelines of the global initiative for asthma(GINA).
- Explain why short acting β2-agonists are 1st choice bronchodilators.
- Explain why antimuscarinics are alternatives in patients intolerant to β2-agonists or theophylline especially the cardiac & elderly.
- Explain why theophylline is considered a 2nd or 3rd line drug in asthma.
- Explain why inhaled corticosteroids are first choice controllers while oral steroids are reserved for resistant cases.
- Explain why inhalation long acting β2-agonists have to be combined with corticosteroids and are not to be given alone as controllers.
- Explain why leukotriene antagonists are preferred in children.
- Explain why cromolyns are controllers used in mild cases of asthma combined with corticosteroids & are not given during acute attacks.
- Describe the lines of management of status asthmaticus.
- Classify antitussives according to their central or peripherl mechanisms.
- Recall the advantages of dextromethorphan .
- Recognize the dangers of over the counter medication.

RESPIRATORY PHARMACOLOGY

DRUG THERAPY OF BRONCHIAL ASTHMA

- Bronchial asthma is a chronic inflammatory disease of the airways (most commonly allergic), characterized by reversible bronchial obstruction with bronchial hyper-responsiveness.
- Hyper-responsive bronchi constrict easily to a wide range of specific or nonspecific stimuli (triggers) that are too weak to affect non- asthmatics → recurrent episodes of expiratory airflow obstruction with shortness of breath, wheezes, chest tightness & cough, worsening at night & early morning.

Causes of Bronchial Hyper-responsiveness

1. Remodeling

- Remodeling of bronchial wall results from repeated exposure to triggers which results in repeated inflammation & repair of bronchial wall → epithelial damage & exposure of nerves to chemical mediators, collagen deposition & wall thickening with narrowing of bronchial lumen.
- Remodeling → hyper-responsiveness of bronchi which constrict easily to endogenous (Ach & histamine) & exogenous stimuli → recurrent attacks.

2. Autonomic Disturbance

- Bronchial hyper-responsiveness may also be due to:
  1. ↑ Vagal tone.
  2. ↓ β-adrenergic response to stress (↓ circulating epinephrine).

Types of bronchial asthma according to triggers

I. **Antigen-induced asthma** (most common): common allergens include pollens, furred animal (cats, dogs), house dust mites, and cockroaches.

II. **Non-antigen induced asthma**

- Cold air or exercise- induced asthma.
- Viral chest infection-induced asthma.
- Aspirin-induced asthma.
- Asthma associated with COPD [1].

Pathogenesis of Asthma

(Multifactorial)

- Patients with antigen induced asthma have ↑ IgE antibodies (genetic).
- Inhalation of allergen by patients with hyper-responsive bronchi triggers an attack which consists of 2 phases:

I. **Immediate Phase** (bronchospasm):

- Starts 10 min after exposure to antigen, reaches a maximum at 30 min & resolves within 1 to 3 hours, spontaneously or with treatment.
- Exposure to a specific antigen (pollens,....) → antigen-antibody (IgE) interaction at the surface of **mast cells** → release of chemical mediators (histamine, 5-HT & bradykinin - LTs C & D) → bronchospasm.

N.B.: In other types, non-allergic factors (virus, cold, aspirin,...) serve as triggers.

---

[1] COPD (chronic obstructive pulmonary disease): an inflammatory disease which is mainly due to smoking & pollution. It is characterized by airflow limitation that is not fully reversible. It includes emphysema, (destruction & distention of alveoli); chronic bronchitis (chronic cough & sputum; mucus hyper-secretion) and small airways disease (small bronchioles are narrowed) → chronic cough, dyspnea & wheezes with chest hyperinflation & diaphragmatic fatigue.

II. Late Phase (sustained bronchospasm & inflammation)

- Due to continuous antigen exposure or refractory bronchoconstriction; starts 3 hrs after exposure, is maximum in 8 hours & resolves in 24 hrs.
- Continued exposure to antigen or other triggers also releases cytokines (interleukins - TNF_α...) from lymphocytes & mast cells → attraction & activation of neutrophils & eosinophils in bronchial mucosa → release of inflammatory mediators (LTs - PGD_4 – TXA_2 - PAF- adenosine) →

1. Sustained bronchoconstriction.
2. Thickened mucosa due to:
   VD - edema - inflammatory cell influx.
3. Hyper-secretion of viscid mucus in lumen.

Clinical Picture

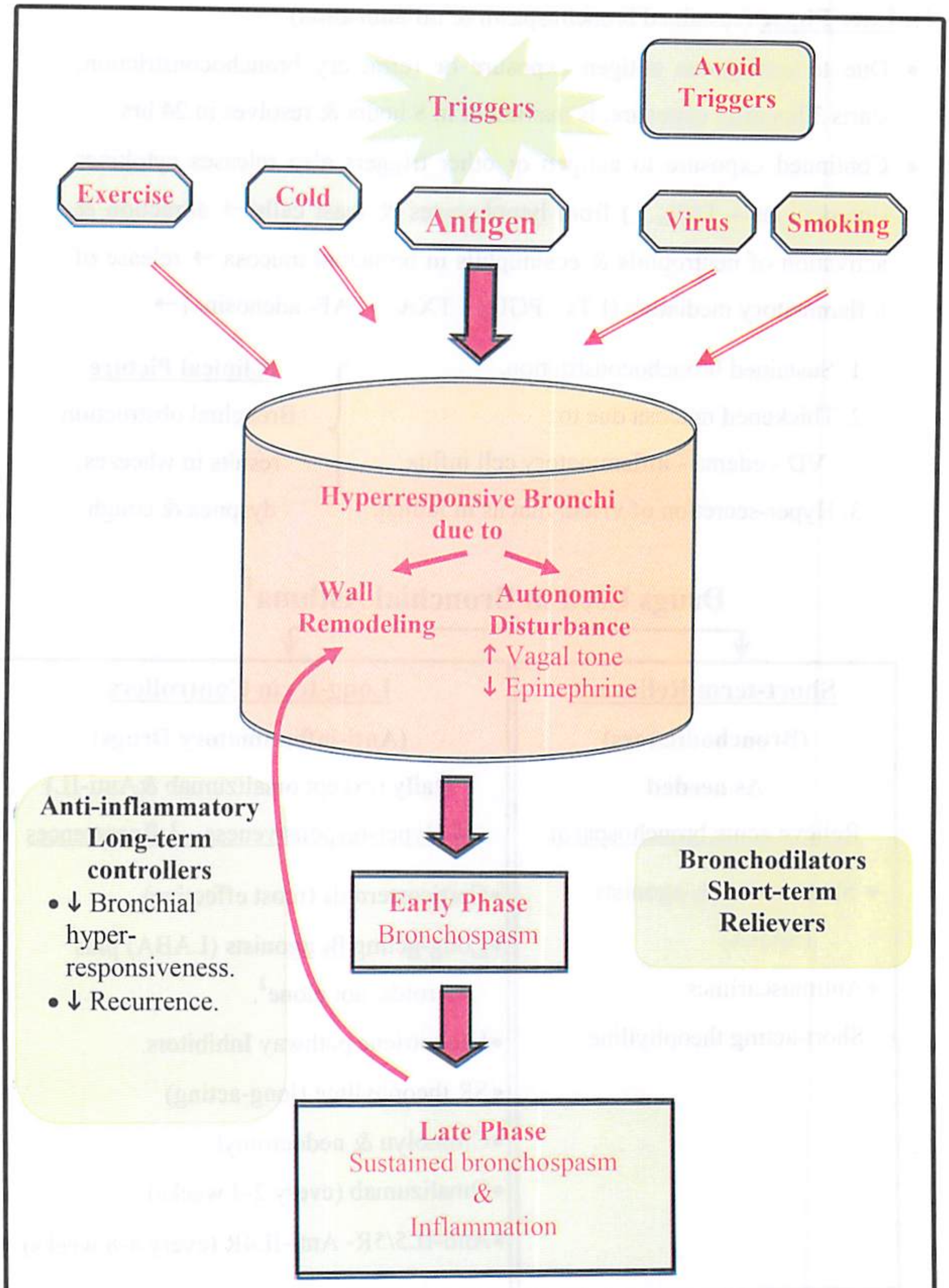
Bronchial obstruction results in wheezes, dyspnea & cough.

Drugs Used in Bronchial Asthma[1]

Short-term Relievers	**Long-term Controllers**
(Bronchodilators)	**(Anti-inflammatory Drugs)**
As needed	**Daily** (except omalizumab &Anti-IL)
Relieve acute bronchospasm	↓ Hyper-responsiveness - ↓ Recurrences
• Short-acting β_2-agonists (SABA)	• Corticosteroids (most effective).
• Antimuscarinics.	• Long-acting β_2 agonists (LABA) plus steroids, not alone[2].
Short-acting theophylline.	• Leukotriene pathway Inhibitors.
	• SR theophylline (long-acting)
	• Cromolyn & nedocromyl.
	• Omalizumab (every 2-4 weeks).
	• Anti-IL5/5R- Anti-IL4R (every 4-8 weeks)

---

[1] LABA are 1st choice "add - on therapy" to steroids, given separately or in a combination inhaler device. Adding LABA, theophylline or LT antagonists ↓ need for increasing corticosteroid dose.


Triggers
Avoid Triggers
Exercise
Cold
Antigen
Virus
Smoking
Hyperresponsive Bronchi due to
Wall Remodeling
Autonomic Disturbance
↑ Vagal tone
↓ Epinephrine
Anti-inflammatory Long-term controllers
• ↓ Bronchial hyper-responsiveness.
• ↓ Recurrence.
Early Phase
Bronchospasm
Bronchodilators Short-term Relievers
Late Phase
Sustained bronchospasm & Inflammation

Pathophysiology of Bronchial Asthma & its Management

Classification of Asthma[1] & its Management

Intermittent
"Controlled Asthma"

Persistent
(mild, moderate, severe)
"Partly controlled & uncontrolled

5 step strategy for management of asthma (according to severity)

Step 1: (for controlled asthma).

- As needed Low dose ICS (budesonide)- formoterol.
- **Alternatives:**
  - Low dose ICS whenever SABA is taken.

Step 2

- **Initially:**
  - Low dose ICS.
  - **OR** As needed Low dose ICS (budesonide)- formoterol.
- **Alternatives:**
  - LT antagonist.
  - Low dose ICS whenever SABA is taken.

Step 3

- **Initially:** Low dose ICS + LABA.
- **Alternatives:**
  - Medium dose ICS
  - Low dose ICS + LT antagonists.

> **As-needed reliever in all steps:**
> low dose ICS/ formoterol as formoterol has rapid onset with rapid relief.
> **Alternative:**
> Short acting β2 agonist (SABA)

---

[1] Asthma is classified into: intermittent & persistent (mild, moderate& severe) according to:

i. **Broncho-constrictive episodes**: < 2 days /week, > 2 days/week but not daily, daily, continual, respectively.
ii. **Night time symptoms**: <2 days/ month, 3-4 times/ month, > 1 time/week but not daily, sometimes every night, respectively.
iii. **Peak expiratory flow:** near normal in intermittent & mild persistent, 60-80% of normal in moderate persistent and <60% of normal in sever persistent.

Step 4

- **Initially:** Medium dose of ICS + LABA.
- **Alternatives:**
  - High dose ICS.
- **Add-on:**
  - Tiotropium (≥ 6 years).
  - **OR** LT antagonist.

Step 5

- **Initially:** High dose of ICS + LABA.
- **Add-on:**
  - Tiotropium.
  - Anti-IgE (omalizumab) (≥ 6 years).
  - Anti-IL5 /Anti-IL5R[2]
  - Anti-IL4R (≥ 12 years)[3].
  - Other controller: add-on Oral CS but consider side effect.

NB.:

- Cromolyn & nedocromil sodium are **rarely used.** May be used in long-term control of **mild persistent** asthma (plus ICS); never alone.
- Theophylline is not recommended by several guidelines especially in children below 12 years.

---

[2] Anti-IL5: mepolizumab (SC) (≥ 12 years), reslizumab (IV) (≥ 18 years).
- Anti-IL5R: benralizumab (SC) (≥ 12 years).
Uses: add-on therapy" in severe uncontrolled allergic asthma uncontrolled on high dose ICS/LABA. **Adverse effects:** headache, injection site reaction.

[3] Duplimab (SC). Add-on therapy" in severe uncontrolled allergic asthma uncontrolled on high dose ICS/LABA or requiring maintenance OCS. **Side effects:** injection site reaction, eosinophilia.

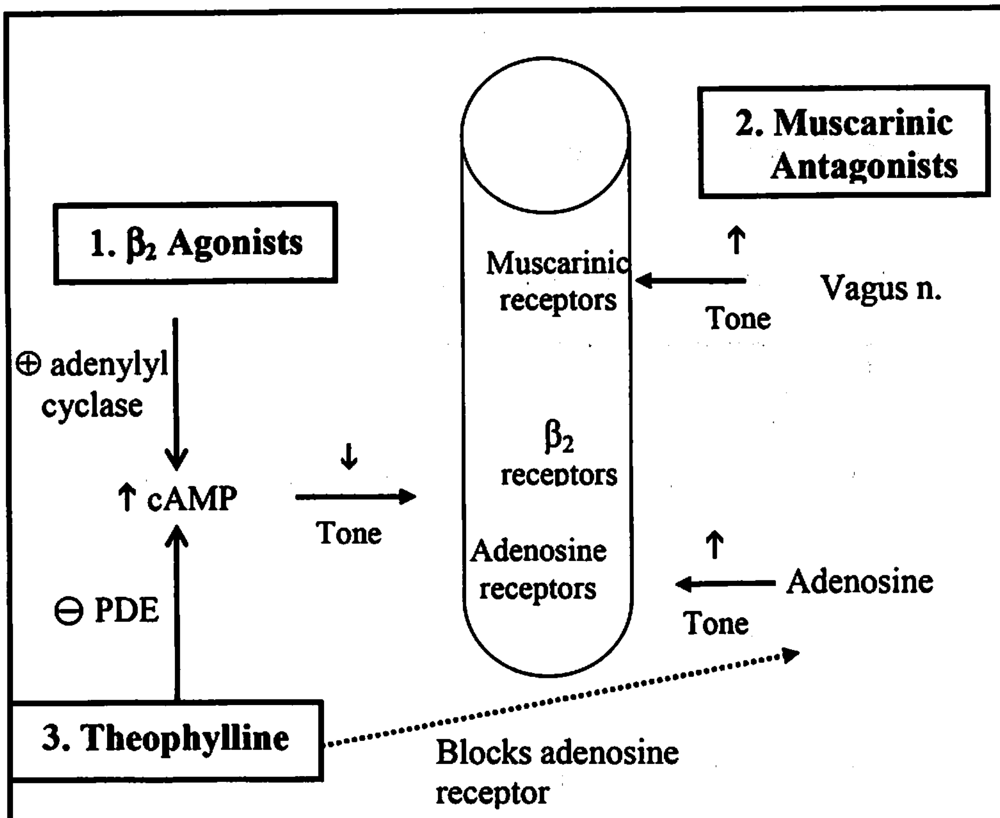
Individual Drugs

A. Bronchodilators

1. Adrenoceptive Agonists.

2. Antimuscarinics.

3. Methylxanthines (Theophylline).


2. Muscarinic Antagonists
1. β_2 Agonists
Muscarinic receptors
↑ Tone
Vagus n.
⊕ adenylyl cyclase
β_2 receptors
↑ cAMP
↓ Tone
Adenosine receptors
↑ Tone
Adenosine
⊖ PDE
3. Theophylline
Blocks adenosine receptor

Control of Bronchial Tone & Site of Action of Bronchodilators

- Bronchial tone is relaxed by circulating epinephrine acting on β_2 receptors (no adrenergic innervation).
- NO is the main inhibitory neurotransmitter for bronchial smooth muscle.

1. Adrenoceptor Agonists

Selective β_2 Agonists

Mechanisms of Action

- Stimulate β_2 receptors increasing intracellular cAMP. They induce:
  1. Bronchodilation.
  2. Inhibition of release of mast cell mediators & cytokines.
  3. Increased bronchial mucociliary clearance.
- Long acting β_2 agonists (LABAs) potentiate anti-inflammatory effects of corticosteroids (↑nuclear localization of steroid receptor) → ↑ asthma control.

Classification & Uses of Selective β_2 Agonists [8]

Short-Acting	**Long-Acting**
Salbutamol (albuterol) -Terbutaline	**Salmeterol - Formoterol**
(Inhalation– oral - IV)	(Inhalation)
• Rapid onset & short acting (4 hrs) → used as short-term relievers by inhalation ("as needed") in: 1. Asthma. 2. COPD.	• Slower onset & long acting (12 hours) → used as control medication in: 1. Asthma (+ corticosteroids). 2. COPD (maintenance).
• Prophylactic in exercise induced asthma (inhaled 10 min before exercise).	• Prophylactic in exercise induced asthma (inhaled 1 hour before exercise → longer protection).

---

[8] Short acting oral β_2 -agonists are used in children who cannot use inhalers.
Long acting agents are lipid soluble → dissolve in smooth muscle membrane.
Formoterol (rapid onset) → can be also used as rescue medication (+ ICS).

Adverse Effects of Selective β_2 Agonists (less with inhalation therapy)

1. Tremors (most common) - anxiety.
2. Tachycardia (high conc. → stimulate β_1 receptors).
3. Tolerance; down regulation of β receptor with regular use.
4. Hypokalemia and muscle cramps
5. Hypoxemia: if lung ventilation/perfusion ratio worsens (β_2 stimulation → vasodilation more than bronchodilation → insufficient blood oxygenation).

N.B.:

- Inhalation LABAs (salmeterol, formoterol) are commonly given in a combination inhaler device with corticosteroids since they should not be given alone as controller medication as their anti- inflammatory effect is insignificant & their bronchodilator effect masks the progression in asthma severity →↑ **risk of mortality.**
- Oral LABAs (SR salbutamol, SR terbutaline & **bambuterol**, prodrug of terbutaline) may be used as controllers if additional bronchodilation is needed.

Non-selective Adrenoceptor Agonists

Epinephrine ($\alpha\ \beta_1\ \beta_2$)

- Largely replaced by selective β_2 agonists due to:
  - Shorter action.
  - Non-selectivity →
    1. β_1 effect → dangerous tachycardia & arrhythmia.
    2. α Effect →↑ BP
- Mainly used in acute attacks of bronchospasm especially in anaphylaxis (→ rapid β_2 bronchodilation, β_1 cardiostimulant & α_1 VC; decongestant effects).

Ephedrine

- Rarely used due to CNS side effects & availability of more effective agents.

2. Antimuscarinic Drugs

Members

Short-Acting
Ipratropium

Long-acting
Tiotropium

- Atropine substitutes; antagonists on bronchial muscarinic receptors.
- Given by inhalation alone or with β_2 agonists, with minimal systemic adverse effects of atropine (quaternary compounds poorly absorbed).

Mechanism of Action

- Block M_3 receptors in bronchial musculature → blockade of vagally-mediated bronchospasm and mucus secretion.

Indications of Ipratropium

1. Bronchodilator of choice in:
   - Asthma induced by psychogenic stimuli or β-blockers.
   - Asthmatic patients intolerant to the tachycardia or anxiety of β_2-agonists or theophylline especially cardiac, elderly & thyrotoxic patients.
2. Acute severe asthma (adjuvant to β_2 agonists).
3. COPD (responds better than asthma[9]).

Disadvantages of ipratropium

1. Tolerance: blocks presynaptic M_2 receptors on cholinergic nerve terminals → ↑ACh release, reducing its effectiveness.
2. Delayed onset of action & less effective than β_2 agonists in asthma.

Tiotropium

- Long-acting antimuscarinic used as maintenance therapy in COPD.
- **Advantage**: its use is not associated with tolerance.

---

[9] Since vagal- induced bronchospasm is the only reversible cause of bronchial obstruction in COPD.

3. Methylxanthines

- Methylxanthines include: caffeine, theophylline and theobromine that are present naturally in coffee, tea, cola, cocoa and chocolate.
- Caffeine is more selective on CNS & cerebral vessels while theophylline is more selective on smooth muscles.

Mechanisms of Action (not completely understood)

1. Inhibit phosphodiesterases → ↑ intracellular cAMP resulting in:
   a. Direct bronchodilation.
   b. Anti-inflammatory →
      - ↓ Mast cell mediators release.
      - ↓ Cytokines → inhibit late asthmatic response.
2. Block adenosine receptors → bronchodilation.

Pharmacokinetics

- Xanthine bases and their salts are absorbed from GIT.
- 90 % metabolized in the liver by cytochrome p 450.
- Saturable kinetics→↑ risk of toxicity

Factors Affecting Theophylline Clearance Requiring Dose Adjustment

$t_{1/2}$ & Serum level ↑↑ in	**$t_{1/2}$ & Serum level ↓↓ in**
• Neonates & elderly.	• Children.
• Hepatic disease & heart failure.	• Heavy smokers.
• Viral infections.	• Heavy drinkers
• **Enzyme inhibitors:**	• **Enzyme inducers:**
Erythromycin- oral contraceptives	Rifampicin - phenobarbital,
Ciprofloxacin -zileuton-zafirlukast.	phenytoin - carbamazepine.
↓ Dose	↑ Dose

Actions- Adverse Effects & Precautions of Theophylline

Pharmacological Actions	**Adverse Effects - Precautions**
1. **Anti-asthma effect** • Bronchodilation → relieve acute bronchospasm. • Anti-inflammatory (modest effect) → control chronic asthma.	
2.**Skeletal muscle** • ↑ Contractility & reverse fatigue of diaphragm in COPD→ ↓ dyspnea.	
3. **CNS stimulation** • Alertness- insomnia – nervousness. • Tremors - convulsions (high dose). • Respiratory stimulant.	• Headache. • Insomnia- Anxiety. • Convulsions.
4. **CVS** • +ve inotropic & chronotropic → sinus tachycardia & arrythmia (high dose). • Vasodilation in high doses → hypotension [10]. • VC of cerebral blood vessels.	• Tachycardia & arrhythmias. • Cardiac arrest[11]→give slowly IV. • Hypotension.
5. **GIT** • ↑ HCl. • Gastric irritation.	• Anorexia- nausea ,vomiting (give with meals; CI peptic ulcer. • Proctitis (suppositories).
6. **Kidney**: weak diuretic action.	
7. ↑ **Risk of toxicity:** • Narrow safety margin & saturation kinetics.	Monitor serum level → adjust dose (see kinetics).

---

[10] Low dose caffeine in soft drinks →↑ CA→ VC →↑ peripheral resistance → slight ↑ BP.

[11] Cardiac arrest is due to stimulation of cardio-inhibitory center.

Disadvantages of theophylline

Theophylline is considered a 2nd or 3rd line drug in asthma due to:

1. Saturation kinetics requiring drug monitoring **(therapeutic level 10-20 mg/L)**.
2. Narrow safety margin.
3. ↑ Risk of drug interactions.

Advantages of theophylline

1. Cheap.
2. Can be given by many routes.

Indications

1. Bronchial asthma (as a 2nd or 3rd line drug)
    - i. Short-term relief of acute bronchospasm (short-acting preparations).
    - ii. Long-term control, especially nocturnal asthma (SR Theophylline).
    - iii. Acute severe asthma.
2. COPD (bronchodilator & reverses diaphragmatic fatigue).
3. Respiratory stimulant in neonatal apnea (caffeine is also used)

Preparations

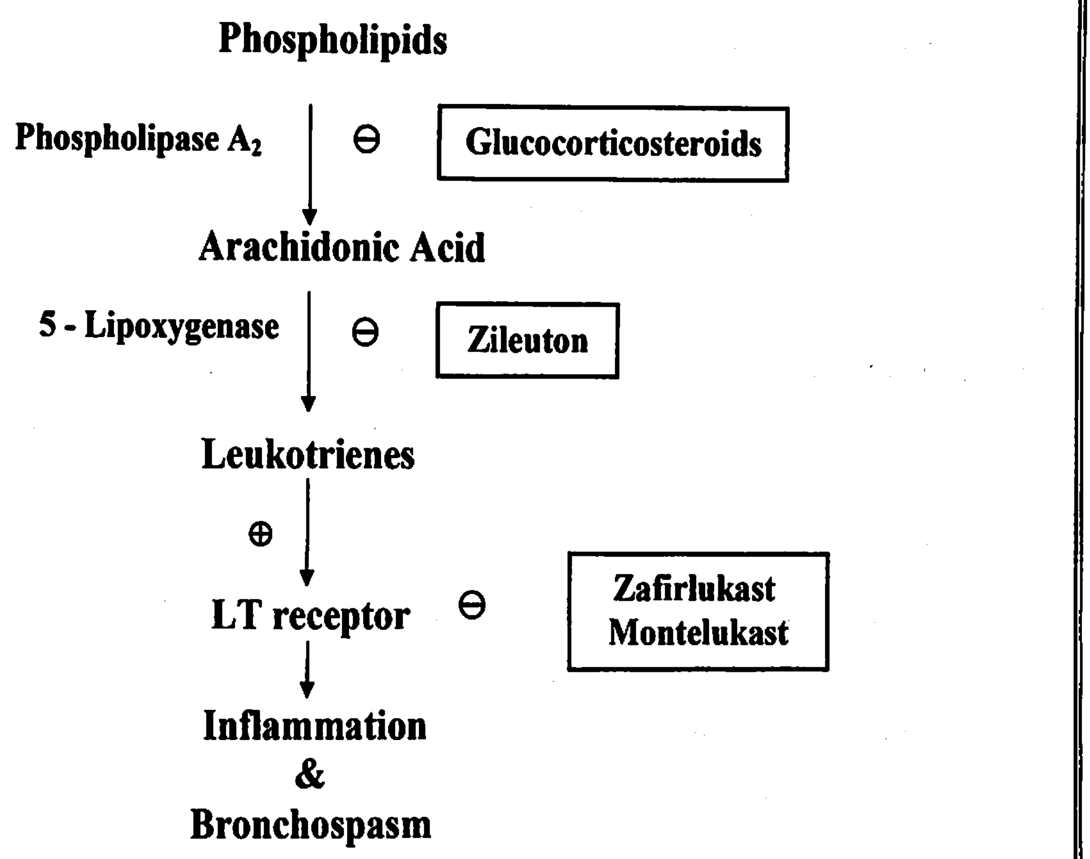
- **Aminophylline** is a combination of theophylline & ethylenediamine to increase its solubility. Can be given by many routes: orally, rectally or slowly IV (loading dose followed by IV infusion).
- **SR Theophylline**: slow-release preparations are long-acting (given orally once or twice/ day) → less fluctuation of plasma level - effective as control medication & in nocturnal dyspnea.
- **Low dose theophylline:** provides full anti-inflammatory effect → less frequent side effects → no need to monitor level.

B. Anti-inflammatory Drugs

- The goal of asthma treatment is to achieve and maintain clinical control (by suppressing inflammation using long term controller medication).

Long term controllers include

1. Glucocorticoids.
2. Long-acting β_2 agonists plus steroids, not alone.
3. Leukotriene pathway inhibitors:
    - 5-Lipo-oxygenase inhibitors → Zileuton.
    - LT Receptor antagonists → Zafirlukast - Montelukast.
4. SR Theophylline.
5. Cromolyn & nedocromil.
6. Omalizumab.


Phospholipids
Phospholipase A2
⊖
Glucocorticosteroids
Arachidonic Acid
5 - Lipoxygenase
⊖
Zileuton
Leukotrienes
⊕
LT receptor
⊖
Zafirlukast
Montelukast
Inflammation
&
Bronchospasm

Anti- inflammatory Drugs Acting on Arachidonic Acid pathway

1. Glucocorticoids

Mechanism of Action

1. Immunosuppressive & anti-inflammatory

- ↓ Cytokines & inhibit phospholipase A_2→ ↓ influx of inflammatory cells & ↓ mediators release → ↓ bronchial inflammation & hyper-responsiveness → ↓ recurrence of attacks.

2. Potentiate β_2 agonists

- ↓ Tolerance to β_2 agonists by ↓ down regulation of β_2 receptors.

Indications in Asthma (mainstay of asthma therapy)

1. Control Medication
   - Given by inhalation.
   - Severe cases may require oral administration (in early morning to coincide with circadian rhythm of CS to ↓ adrenal suppression).
2. Rescue medication in acute exacerbations not responding to β_2 agonists (oral 7-day course).
3. Acute severe asthma. (oral or IV).

Preparations and Routes of Administration

1. Inhalation:

Beclomethazone - budesonide – fluticasone – mometasone.

Ciclesonide:

- Prodrug, activated by bronchial esterases.
- High 1st pass metabolism & tight plasma protein binding → less systemic side effects
- Less frequent candidiasis.

2. Oral: prednisone - prednisolone.

3. Parenteral: methylprednisolone - hydrocortisone.

Adverse Effects

	Minimized by:
1. Oropharyngeal candidiasis. 2. Hoarseness of voice.	- Gargling & spitting following inhalation. - Use “spacer device”.
3. Cataract - glaucoma. 4. Osteoporosis 5. Retardation of growth. 6. Hypertension. 7. Diabetes. 8. Cushing syndrome. 9. Adrenal suppression.	Systemic side effects with oral therapy, reduced by inhalation.

2. Leukotriene Pathway Inhibitors

Mechanism of Action

Zileuton

- 5-Lipooxygenase inhibitor → ↓ LTs synthesis.
- Not commonly used due to liver toxicity & frequent dosing[12].

Zafirlukast-Montelukast

- LTs receptor antagonists → bronchodilation & anti-inflammatory effect.

Indications

1. Control medications in persistant asthma
    - **Alternatives** to inhaled steroids in mild persistant asthma (for patients intolerant to steroids or cannot use inhalers)
    - **Added** to steroids in moderate or severe persistant asthma.
2. Drug of choice for control of aspirin-induced asthma (responds well to LTs antagonists since it is due to ↑ LTs production from arachidonic acid through lipooxygenase pathway following blockade of cyclooxygenase pathway by aspirin).
3. Inhibit exercise-induced asthma if given before exercise.

Advantages

1. Oral therapy (easier than inhalation especially in children).
2. Long duration of action.
3. Well tolerated (minimal side effects).

Adverse Effects

1. Headache.
2. Dyspepsia.
3. Drug interactions due to enzyme inhibition (zafirlukast).

---

[12] A controlled release preparation for twice daily administration is now available.

3. Cromolyn & Nedocromil Sodium

Mechanism of Action (weak anti- inflammatory)

1. Inhibit mast cells degranulation → inhibit release of mediators → inhibit early response to antigen (**mast cell stabilizers**).
2. Inhibit eosinophil activation → inhibit late inflammatory response to antigen.

Actions & Uses (aerosol or microfine powder)

- **Prophylactically:** Inhibit antigen & exercise-induced asthma if inhaled shortly before exercise or before an unavoidable exposure to an antigen (ineffective during an acute attack).
- **Chronic use** (4 times /d): long-term control of **mild persistent** asthma (plus ICS) → ↓ bronchial hyper-responsiveness → ↓ recurrence of acute attacks.
- **Other uses:** allergic rhinoconjunctivitis (nasal spray/eye drops).

Adverse Effects (limited to site of administration as it is poorly absorbed)

1. Throat irritation - cough - bronchospasm (with microfine powder; ↓ by prior inhalation of β_2 agonists).
2. Stinging in the eye (with eye drops).

Ketotifen (related to cromolyn)

- Mast cell stabilizer & antihistamine; infrequently used in asthma.

4. Omalizumab

- Humanized anti IgE monoclonal antibody.
- Binds to **circulating** IgE → inhibits binding of IgE to mast cells.
- Used subcutaneously[13] as "add-on therapy" in severe uncontrolled allergic asthma (↑↑IgE)→ ↓ frequency & severity of exacerbations.

Adverse Effects: ↑ risk of anaphylaxis.

---

[13] Every 2 or 4 weeks.

Management of Acute Exacerbations

- Acute exacerbations may be mild moderate or severe.

1. **Mild acute Exacerbation**
   - Give inhaled short acting β2 agonists[14]
2. **Moderate acute Exacerbation**
   - Add oral corticosteroid (for 5-7 days) if incomplete response to β2 agonists & continue the β2 agonist.
3. **Severe acute Asthma** (Status Asthmaticus)
   - A severe acute attack precipitated by infection, emotions or allergy.
   - It is refractory to the usual lines of treatment due to down regulation of β receptors, mucus plug and acidosis.
   - It is an emergency condition requiring hospitalization for:
     1. Endotracheal intubation and suction of bronchial secretion.
     2. Humidified oxygen inhalation.
     3. IV fluids, correction of acid-base balance, electrolytes & dehydration.
     4. **Drug therapy includes**[15]
        - a. Salbutamol inhalation[16] ± ipratropium inhalation.
        - b. Systemic glucocorticosteroids:
          - -Oral prednisone (if patient can swallow) continue for 5-7 days.
          - -Methylprednisolone IV injection (switch to oral when possible).
        - c. Aminophylline IV infusion (may also be given in severe cases???).
        - d. Artificial respiration (if no response)[17].
        - e. Antibiotics for infection - avoid sedatives (depress respiration).

---

[14] Up to 3 doses of 2-4 puffs at 20 min intervals, then /3 hrs for 24-48 hrs.

[15] Mg sulphate may be used intravenously in patients who failed to respond to other drugs

[16] Salbutamol may also be given iv

[17] Halothane may be given to induce bronchodilation

Respiratory Stimulants

A. Specific Stimulants (specific antagonists)

- **Flumazenil**: reverses benzodiazepine - induced respiratory depression.
- **Naloxone**: reverses morphine - induced respiratory depression.

B. Nonspecific stimulants (analeptics)

- Awaken patients from deep sleep & anesthesia, stimulate respiratory center (directly or reflexly) & induce convulsions in high doses.

Members & Uses

- ☐ **Doxapram** (largely replaced by artificial respiration → safer) used in:
  1. Acute respiratory failure in COPD with hypercapnea & drowsiness.
  2. Postoperative respiratory depression (accelerates post anesthetic recovery).
- ☐ **Caffeine – aminophylline:** in neonatal apnea.
- ☐ **Irritant NH_3 vapor**: in psychotic fainting (stimulates olfactory nerves → reflex stimulation of respiratory center.

Drugs Contraindicated in Bronchial Asthma

&

COPD

1. β-blockers: propranolol................
2. Histamine liberators: morphine, hydralazine, tubucurarine...
3. NSAIDs: aspirin, indomethacin.........
4. Cholinomimetics: neostigmine..........

DRUG THERAPY OF COUGH

- Cough is a physiological protective reflex through which excessive bronchial secretion (mucus) or foreign bodies are expelled outside respiratory tract.
- It occurs due to stimulation of irritant cough receptors in respiratory passages or outside (esophagus, heart or ears).
- Cough reflex is controlled by cough center in the medulla.

Management of cough:

I. **Specific treatment**: treatment of cause.

II. **Nonspecific treatment**: antitussives - mucolytics – expectorants.

- Nonspecific drug therapy is indicated if cough is not resolved, causing insomnia, fatigue or bladder incontinence or in patients undergoing eye surgery.

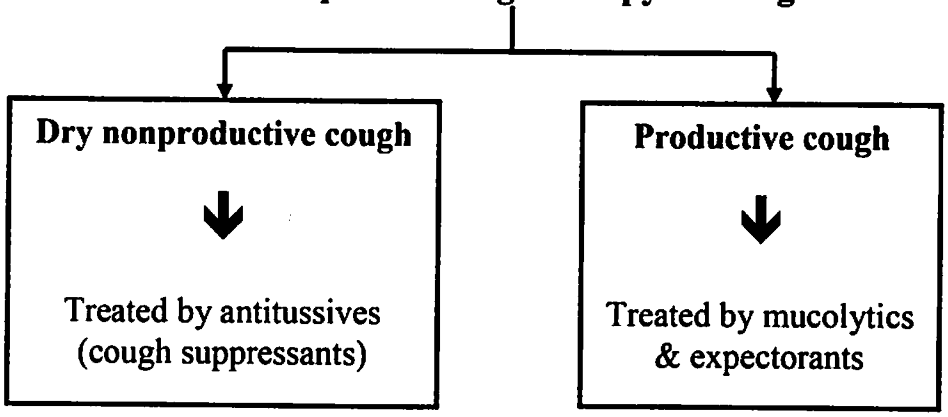
Causes of cough & their Specific Therapy

1. **Acute cough**[18]: upper respiratory viruses irritating respiratory tract receptors.
2. **Chronic persistent cough**:
   - **Smoking** → stop smoking to avoid bronchial irritation & mucus hypersecretion.
   - **Rhinosinusitis** → decongestants & antihistamines → ↓ postnasal discharge (drip) irritating cough receptors.
   - **Asthma – COPD** → bronchodilators.
   - **Reflux esophagitis** → anti-reflux drugs reduce reflux of HCl thus reducing its stimulatory effects on cough receptors in esophagus.
   - **ACE inhibitors** → nifedipine; calcium channel blocker.
   - **Other causes of chronic cough:** lung tumors…

---

[18] Cough lasting < 3 weeks. It stops after infecton resolves.

Nonspecific Drug Therapy of Cough


Dry nonproductive cough
Treated by antitussives (cough suppressants)
Productive cough
Treated by mucolytics & expectorants

Antitussives (Cough Suppressants)

A. Central Antitussives (in moderate to severe cough)

I. Opioid antitussives:

1. Codeine

- Opioid antitussive with moderate analgesic effect.
- Inhibits cough center in the medulla.

Side Effects

a. Drowsiness.

b. Paradoxical excitement (in children below 6 years).

c. Mild dependence.

d. Constipation (on chronic administration).

e. Respiratory depression (when used in large doses as analgesic).

2. Pholcodeine

- Semisynthetic opioid derivative with fewer adverse effects than codeine.

3. Dextromethorphan

- Selective opioid antitussive, inhibiting cough center in medulla.
- Preferred to codeine due to reduced liability for dependence , constipation or respiratory depression (in antitussive doses).

II. Antihistamines (Diphenhydramine)

- Sedative antitussives (sedation reduces sensitivity of cough reflex).
- Anticholinergic effect contributes to antitussive effect therefore better than newer generations of antihistamines.
- **Side effects**: sedation - anticholinergic effects (dryness of secretion).

> - In bronchiectasis (suppurating bronchial inflammation) or chronic bronchitis, antihistamines→ harmful sputum thickening & retention. Thus mucolytics are used.

B. Peripheral Antitussives

- Used to treat mild & moderate dry cough, e.g. sore throat & laryngitis.

1. Volatile oils (menthol and camphor) and liquorice

- Protect respiratory tract irritant receptors by a mucin layer (demulcents).
- Given as lozenges or compressed tablets that dissolve in mouth.
- May be inhaled in a hot steam.

2. Benzonatate

- Has local anesthetic effect on pulmonary stretch receptors and irritant receptors in respiratory mucosa.

N.B.: Cough syrup or glutinous sweets with no cough medication possess a soothing effect on irritant receptors (demulcents).

Treatment of Productive Cough

1. Expectorants

- Expectorants liquefy bronchial secretion by increasing its volume (except aromatic) & reducing its viscosity, thus facilitating sputum removal through coughing.
- They stimulate bronchial secretion either directly by acting on bronchial glands or reflexly through gastric irritation.

Members

1. **Guaifenesin**: gastric irritant; given with a full glass of water.
2. **Aromatic**: volatile oils in water vapor: menthol - tinc. benzoin or tolu.
3. **Nauseant**: syrup ipecac – ammonium chloride or carbonate.
4. **Alkaline**: Na^+, K^+ acetate or citrate.
5. **Na^+ & K^+ Iodides**:
    - Expectorants: stimulate bronchial glands directly & reflexly.
    - Mucolytics: enhance proteolytic enzymes in mucus.

Adverse Effects of iodides

1. Respiratory irritation (**CI:** acute bronchitis & asthma).
2. Gastric irritation
3. Hypersensitivity.
4. Iodism: excessive secretions of exocrine glands (lacrimal, salivary…).
5. Spread of infection in TB (**CI:** TB bronchitis).

2. Mucolytics

- Mucolytics decrease viscosity of bronchial secretion; potentiating expectorants.

Mechanism of Reduction of Mucus Viscosity by Mucolytics

Acetylcysteine
Carbocystiene

- Break disulfide bonds of thick mucus.

Bromhexine

- Depolymerizes mucus mucopolysacharide ground substance.

Indications of Mucolytics (oral - inhaled or instilled in tracheostomy tube)

1. **As mucolytics in**:
   - Asthmatic bronchitis - COPD – Bronchiectasis.
   - Pulmonary cystic fibrosis[19] - Care of tracheostomy.
2. **Paracetamol toxicity**: acetylcysteine (supplies liver with SH-group to conjugate paracetamol metabolites).

Adverse Effects of Mucolytics

1. Gastric irritation.
2. Hypersensitivity
3. Bronchospasm (acetylcysteine).

Water vapor inhalation is an excellent expectorant and mucolytic.

---

[19] Dornase alpha (recombinant Human DNase): a mucolytic that cleaves DNA of invading neutrophils in mucus is used in cystic fibrosis.

Cough Mixtures and Cold Remedies

- Cough mixtures and cold remedies are over the counter medications (OTC) used in cases of common cold and cough.
- **They contain several of the following ingredients:**
    - Antitussives → dextromethorphan.
    - Expectorants → guaifenesin.
    - Mucolytic → bromhexine.
    - Bronchodilators → salbutamol.
    - Decongestants → phenylephrine – pseudoephedrine - nasal oxymetazoline- naphazoline.
    - Antihistamines → diphenhydramine.
    - Analgesics →paracetamol (caffeine may be added as adjuvant).

Disadvantages of Cough mixtures and Cold remedies

1. The use of unnecessary medications in the mixtures (it is better to treat each symptom of common cold separately).
2. Hidden[20] ingredients may be dangerous or may result in drug interactions:
    - Decongestant sympathomimetics are dangerous in hypertensives or may increase BP dangerously in patients on MAOIs.

---

[20] Their presence in the preparation may not be expected.

V. GASTROINTESTINAL PHARMACOLOGY

Intended Learning Outcomes (ILOs)

By the end of this chapter, the student should be able to:

- Identify different groups of drugs used in peptic ulcer disease and describe their mechanisms of action & adverse effects.
- Discuss the advantages of proton pump inhibitors over H2 antagonists.
- List different drugs used in various types of vomiting and identify the receptors with which they interact.
- Recognize the importance of metoclopramide as a widely used antemetic, its adverse effects & the advantages of domperidone over it.
- Identify at least 2 drugs commonly used as antidiarrheal agents.
- List 4 drugs with different mechanisms of actions that are used as laxatives.
- Discuss the choices of drugs used in different causes of constipation.
- Discuss the choices of drugs used in irritable bowel syndrome according to its different presentations.
- Discuss the different mechanisms by which drugs used in bleeding esophageal varices act.

GASTROINTESTINAL PHARMACOLOGY

DRUG THERAPY OF ACID - RELATED GIT DISEASES

- Acid-related GIT diseases occur in 25% of adult people. They are induced or aggravated by gastric HCl. The most important of these diseases are:

  A. **Peptic Ulcer** **(PU)**

  1. Duodenal ulcer (DU): the most common type; caused by ↑ HCl & chronic *Helicobacter pylori (H. pylori)* infection.
  2. Gastric ulcer (GU): usually caused by chronic NSAIDs therapy.
  3. Stress ulcer: caused by severe medical or surgical stress.
  4. Zollinger-Ellison syndrome: ↑ HCl secretion by a gastrin- producing tumor → multiple ulcers.

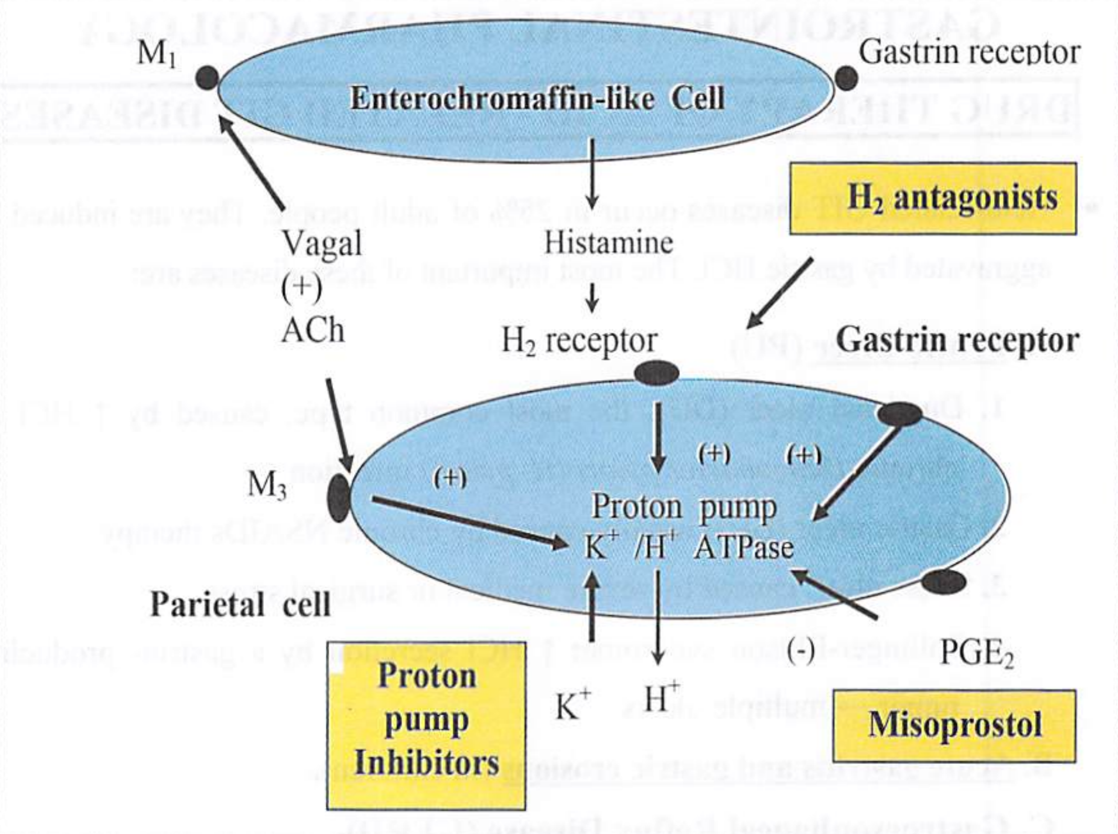
  B. **Acute gastritis and gastric erosions** (in children).

  C. **Gastroesophageal Reflux Disease** **(GERD)**

  - More common than peptic ulcer.
  - Reflux symptoms (e.g. heart burn) occur in 50% of people.

Regulation of HCl Secretion

- The parietal cells in gastric mucosa contain receptors for the three main stimulants for HCl secretion: gastrin (G), histamine (H_2) & ACh (M_3)
- Activation of M_3 & gastrin receptors on parietal cells →↑intracellular Ca^{2+} → ⊕ proton pump (K^+/H^+ ATPase) →↑ HCl secretion.
- Activation of M_1 & gastrin receptors on gastric enterochromaffin like (ECL) cells → ⊕ histamine release from ECL cells.
- Released histamine stimulates H_2 receptors on parietal cells → activation of adenylcyclase → ↑cyclic AMP → ⊕ proton pump.
- PGE_2 receptors activation in parietal cells → ↓ histamine-stimulated c-AMP production → ⊖ proton pump → ↓ HCl secretion (PGE_2 is protective).


M1
Gastrin receptor
Enterochromaffin-like Cell
H2 antagonists
Vagal
(+)
ACh
Histamine
H2 receptor
Gastrin receptor
M3
(+)
(+)
(+)
Proton pump
K+ /H+ ATPase
Parietal cell
(-)
PGE2
Proton pump Inhibitors
K+
H+
Misoprostol

HCl secretion & Site of Action of Drugs Inhibiting HCL Secretion

- HCl secretion by proton pump (K^+/H^+ ATPase) is stimulated by gastrin, histamine (H_2) & ACh (M_3) & inhibited by PGE_2.
- M_1 & gastrin receptors on enterochromaffin –like cells release histamine which acts on H_2 receptors on parietal cells →↑cAMP → HCl secretion .

DRUG THERAPY OF PEPTIC ULCER

- Most cases of peptic ulcer are caused by:
  - i. H. pylori infection: a noninvasive, microaerophilic gram-negative organism → ↑ gastrin-induced HCl secretion, gastritis and its toxin induces mucosal damage.
  - ii. Chronic use of NSAIDs.

Integrity of Gastrodudenal Mucosa
Depends on the Balance between

Defensive Mechanisms	Aggressive Mechanisms
• Mucus - bicarbonate.	• HCl - pepsin – bile.
• PGE_2 - blood supply.	• *H. pylori* infection.

Risk Factors for PU

1. Stress.
2. Smoking: ↑ HCl - ↓ bicarbonate - induces VC (leading to ischemia) - antagonizes acid suppressive drugs.
3. Alcohol – caffeine - theophylline (mucosal irritants -↑ HCl)
4. Drugs decreasing PGs: NSAIDs - corticosteroids.

Pathogenesis of Peptic Ulcer & Lines of Treatment

Peptic Ulcer results from an imbalance between aggressive & defensive mechanisms in gastric or dudenal mucosa:

1. ↑ **HCl secretion: treated by** → antisecretory drugs (proton pump inhibitors -H_2 antagonists – anticholinergics & misoprostol) – neutralization of secreted acid (antacids).
2. **Infection with *H. pylori*: treated by** → anti *H. pylori* therapy (antibiotics plus antisecretory drugs with or without bismuth).
3. **Inadequate mucosal defense against HCl: treated by** → mucosal or cytoprotectives (sucralfate, misoprostol and colloidal bismuth).

Treatment of gastric ulcer

1. Treatment **with anti-secretory drugs** is the main line.
2. Mucosal protective drugs & antacids are rarely needed.

Treatment of duodenal ulcer

1. Treatment **with anti-secretory drugs**.
2. ***H. pylori*** eradication therapy.
3. Mucosal protective drugs & antacids are rarely needed.

Anti - secretory Drugs

1. Proton Pump Inhibitors (PPIs)

Omeprazole - Lansoprazole- Pantoprazole - Rabeprazole - Esomeprazole

Mechanism of Action

- Act on the final step of HCl secretion. → **Most effective** acid suppressants.
- They are prodrugs which, upon absorption into circulation, reach parietal cells & are converted in the acid medium in secretory canaliculi, into active form.
- Active form inhibits H^+/K^+ ATPase (proton pump) of parietal cells → inhibits H^+ secretion into gastric lumen → ↓ gastric acid production .
- Inhibit basal & meal stimulated acid secretion (98% , 1-2 h after 1st dose).
- They possess anti- *H. pylori* effect[1] (lansoprazole most potent).

Pharmacokinetics

1. Weak bases destroyed by gastric acidity & ionized in acid stomach (not readily absorbed) →given in enteric-coated form. readily absorbed in alkaline small intestine
2. Should be given about 30- 60 minutes before meals[2].
3. Food ↓bioavailability by 50% (so taken on empty stomach)[3].
4. Repeated administration →↓ gastric acidity → ↑ bioavailability[4].
5. Long duration (onset 1 hour & lasts for 24 hours (t½ = 1h but PPIs bind covalently to PP and synthesis of new pump requires 24 hours.).
6. Metabolized in the liver.

---

[1] 2ry to inhibition of HCl secretion (which potentiates action of antibiotics) & direct inhibition of a P-type ATPase enzyme in the bacteria.

[2] PPIs only inhibit active pumps. However, in a fasting state, only 10% of pumps are actively secreting acid and susceptible to inhibition. **Administer PPIs ~ 1 hour before a meal**, so that peak serum concentrations coincide with maximal pump activity

[3] PPIs **must be administered** in the fasting state, when gastric motility is low. Bioavailability is decreased approximately 50% by food because larger amplitude movements crush the protective coatings, exposing the prodrugs to the stomach acid (which is in high concentration) and causing them to be inactivated.

[4] Preparations of PPIs are either single coated (enclosing the dosage form as a whole) or double coated (coat enclosing drug particles and another enclosing the dosage form). Double coating ensures that the drug is not released in stomach. Preparations with single coating are liable to disintegrate in stomach releasing the drug that is inactivated by gastric acidity . Repeated administration of these preparations→ ↓ gastric acidity → ↑ bioavailability

Adverse effects

1. GIT: abdominal pain, nausea, vomiting, diarrhea or constipation.
2. CNS: headache, dizziness, somnolence.
3. Hypochlorhydria →
   - ↑ Risk of infection (e.g. hospital acquired pneumonia & *H. pylori*).
   - Gastric tumor (in animals): bacterial colonization → ↑carcinogenic nitroso compounds.
4. Vitamin B12 deficiency (long term use)
5. Enzyme inhibition (clinically insignificant).

1. H_2-Receptor Antagonists

Cimetidine – ranitidine – famotidine - nizatidine

Mechanism & Pharmacological Actions

- Reversible competitive antagonists of H_2 receptors on parietal cells.
- Complete inhibition of histamine mediated but partial inhibition of ACh or gastrin mediated HCl secretion.
- Potent inhibition of nocturnal or fasting but less inhibition of daytime (meal-stimulated) acid secretion[5].

Individual H_2 Antagonists

Cimetidine: 1st member developed, but its use is limited due to its enzyme inhibiting, antiandrogenic & CNS side effects.

Newer members developed to minimize adverse effects of cimetidine[6]:

Ranitidine

- More potent than cimetidine, less enzyme-inhibiting & antiandrogenic effects.
- Anti-*H. pylori* effect (most efficient).
- 50% bioavailability (hepatic first pass effect)
- 50% metabolized in liver **(CI in hepatic dysfunction).**

---

[5] Nocturnal HCL secretion depends on HI, meal stimulated secretion depends on gastrin , Ach & HI

[6] Nizatidine: 100% bioavailability (no 1st-pass effect) → used in liver dysfunction. Completely excreted by kidney → CI in renal dysfunction. no enzyme-inhibiting or antiandrogenic effects.

Famotidine

- The most potent.
- Cytoprotective effect.
- 50% decomposed by gastric acidity.
- 50% bioavailability.
- Excreted mainly by kidney (**preferred in liver dysfunction**).
- No enzyme-inhibiting or antiandrogenic effects.

Adverse Effects of H_2 Blockers

1. Headache, diarrhea or constipation.
2. Tolerance, rebound hyperacidity & recurrence (upregulation of H_2 receptors).
3. CNS: sedation, confusion, hallucination[7] (mostly with cimetidine).
4. Antiandrogenic, ↑ prolactin, gynecomastia, galactorrhea, impotence (mostly with cimetidine).
5. Enzyme inhibition → drug interactions (mostly with cimetidine).
6. Hypotension & bradycardia if given rapidly IV in intensive care[8].

Advantages of PPIs over H_2 antagonists:

- Higher efficacy → better symptomatic relief & higher response rates.
- More prolonged effect (≈ 24 hs→ given in single daily dose; versus twice daily dosing with H_2 antagonists).
- More effective in anti H. pylori regimen.

---

[7] Especially in the elderly or in renal or hepatic dysfunction.

[8] Block cardiac H_2 receptors.

Indications of Antisecretory Drugs

1. **Peptic ulcer**
    - PPIs are preferred especially in severe cases.
    - H_2 antagonists in mild or moderate cases (healing is delayed for 8 weeks & recurrence is common).
2. **Anti-** ***H. Pylori*** **regimens**
    - PPIs are preferred.
    - Ranitidine bismuth citrate may be used.
3. **GERD**
    - PPIs are preferred.
    - H_2 antagonists are used to cover the nocturnal HCl secretion.
4. **Zollinger Ellison syndrome**
    - PPI are preferred.
    - High dose of parenteral preparations are given early to cover vomiting period.
5. **Stress ulcer**: to↓ risk of bleeding.
6. Acute gastritis in children & gastric erosions.
7. Bleeding oesophageal varices: to prevent recurrence.
8. To avoid aspiration pneumonia during surgery.[9]

} Parenteral preparations

---

[9] e.g. obstetric anaesthesia before caesarian section.

Mucosal Protectives
(Cytoprotectives)

1. Sucralfate

- It is an aluminium salt of sulfated sucrose.

Mechanism

1. In **acid medium**, the negatively charged sulfate groups bind to the positively charged proteins in the ulcer base, forming a protective barrier against acid, bile and pepsin (also inactivates the latter two).
2. Increases PG synthesis and mucus and bicarbonate secretion.

Uses

- Stress ulcer prophylaxis (mainly).

Adverse Effects

1. Nausea, vomiting and dry mouth.
2. Flatulence, constipation.
3. Al^{3+} toxicity: chelates phosphates → osteomalacia & encephalopathy in renal diseases.[10]

Precautions

- Sucralfate is active only in gastric acid medium, so if antacids or H_2 blockers are given they should be at least 1 hour apart (given on an empty stomach, 4 doses/day; 3 in between meals & one before sleep).
- Binds some drugs (e.g. tetracycline) →↓ absorption, so given at least 2 hours apart.

---

[10] Since normally 5% of the drug is absorbed orally.

2. Misoprostol

Mechanism:

Synthetic PGE_1 analog; cytoprotective through:

- ↓ HCl secretion (by acting on the PG receptors on parietal cells → ↓ histamine-stimulated c-AMP production).
- Increases mucosal blood flow → stimulates mucosal renewal.
- Stimulates secretion of mucus & bicarbonate.

Uses

- Selective for NSAID-induced gastric ulcer (healing effect) if PPIs fail.
- It is also given prophylactically with NSAIDs or corticosteroids.

Adverse effects

- Diarrhea & colic (most common).
- Vaginal bleeding & uterine contractions (CI in pregnancy→ abortion).

3. Colloidal Bismuth

Mechanism

1. Anti-*H. pylori* activity (main effect).
2. Mucosal protective:

Chelates proteins in ulcer base → protective coat against acid & pepsin (& inactivates pepsin) -↑ mucosal bicarbonate , mucus & PG.

Use

- Anti- H. pylori therapy: as ranitidine bismuth citrate which dissociates in stomach into bismuth (anti-*H. pylori* activity) & ranitidine (antisecretory).

Adverse Effects

1. Teeth & tongue discoloration - black stools (confused with bleeding).
2. Encephalopathy and neurotoxicity especially in renal disease.

Do not give for more than 2 months & do not restart within 1 year.

Anti-*H. pylori* Drug Therapy

- Eradication of *H. pylori* infection results in rapid healing & ↓ recurrence.
- It is achieved by combination therapy with:

I. Antimicrobials:

1. Clarithromycin:
    - Of choice due to better acid stability & efficacy (↓ recurrence).
    - In addition to its antimicrobial effect, it ↑ plasma level of ranitidine bismuth citrate (enzyme inhibitor).
2. Amoxicillin.
3. Metronidazole[1] (in patients allergic to amoxicillin), tinidazole.

II. Acid suppressants (PPIs, or ranitidine bismuth citrate)

- Antibiotics alone are ineffective as organism hides inside mucus, under epithelial folds to avoid HCl. If HCl secretion is suppressed; organism comes out, multiplies → ↑susceptibility to antibiotics. Thus high dose acid suppressants are included in anti-*H. pylori* regimens

III. Colloidal bismuth: bismuth subcitrate or subsalicylate.

High efficacy anti-*H. pylori* Triple therapy[2]

- 14 days: Lansoprazole + Clarithromycin + Amoxicillin (or metronidazole)[3].
- Followed by 4-6 weeks: PPI therapy **to allow ulcer heal.**

---

[1] Resistance is common due to ↑ use in amoebiasis.

[2] Quadruple therapy (with added bismuth) may also be used.

[3] Concomitant therapy: PPI + Amoxicillin + Clarithromycin (bid)+ Metronidazole (tid)

Antacids

- Antacids are weak bases that reduce gastric acidity by neutralizing HCl.

Pharmacological Actions

1. Neutralize gastric acid (duration 1-2 hrs).
2. Decrease peptic activity (pepsin is inactive at pH > 4.5).
3. Reduce *H. pylori* colonization.
4. ↑ mucosal PG production (promote defense mechanism).
5. Adsorbent (to pepsin, bile & toxins), astringent[13] and demulcent[14] effects (with Al^{3+} & Mg^{2+} salts only).

Therapeutic Uses (taken 1 and 3 hours after meals & at bedtime)

1. Rapidly relieve pain & help healing of peptic ulcer.
2. Relieve dyspeptic symptoms.
3. GERD (rapid pain relief).

Drug Interactions

- Antacids can affect rates of dissolution, absorption, bioavailability and renal elimination of many drugs through:
    1. Changing gastric or urinary pH.
    2. Delaying gastric emptying.
    3. Chelation:

       Al^{3+} salts can form insoluble complexes with fluoroquinolones, tetracyclines, digoxin and iron salts →↓ absorption (do not give antacids within 2 hrs from administration of these drugs).

---

[13] Precipitate surface proteins.

[14] Soothing effect on the mucous membrane.

Types of Antacids

Local Antacids

Al^{3+} Hydroxide

Disadvantage: constipation.

Mg^{2+} Salts

Disadvantage: diarrhea.

Ca^{2+} carbonate

Disadvantages

1. Constipation.
2. Rebound hyperacidity (Ca^{2+} → acid secretion) → ↓pain relief & healing.
3. Milk-alkali syndrome (systemic alkalosis - hypercalcemia).
4. ↑ CO_2 → flatulance & eructation.

Systemic Antacids

NaHCO$_3$

Advantages

- Rapid onset.
- Potent (↑ pH > 7).

Disadvantages

1. Systemic alkalosis on long-term use.
2. Rebound hyperacidity.
3. Na^{+} content is dangerous in HF, hypertension or renal disease.
4. ↑ CO_2 → flatulence, eructation.
5. Alkaline urine → renal stones.

Choice of antacids[15]

- Al^{3+} hydroxide & Mg^{2+} salts do not result in CO_2 release or systemic alkalosis thus they are the most commonly used antacids, alone or combined (to neutralize the effects of each other on bowel habit).
- Antacids should be cautiously used in elderly & renal impairment since:
  - Al^{3+} antacids → chelate phosphates thus may induce osteomalacia, hypophosphatemia, encephalopathy & ↑ risk of Alzheimer dementia.
  - Mg^{2+} antacids → CNS depression.

---

[15] Sodium bicarbonate is added for effervescent formulations (e.g. with ranitidine) or in immediate release PPI preparations (e.g. with omeprazole).

Precautions to Avoid NSAIDs-induced Ulcer

1. Use low doses and avoid combinations of NSAIDs (↑ toxicity without added benefit).
2. Use topical preparations whenever possible.
3. Co-administer PPIs or misoprostol.
4. Avoid combination with corticosteroids except in selected cases.
5. Use cautiously in the elderly.

DRUG THERAPY OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Pathogenesis of GERD

- GERD involves involuntary regurgitation of gastric acid, pepsin & bile from the stomach to the esophagus.
- The most important responsible mechanism is a defect in esophageal motility → Transient Lower Esophageal Sphincter Relaxations (TLESRs) → regurgitation of gastric contents.
- A defect in gastric motility → delayed emptying & subsequent reflux may also be involved.
- Reflux may be asymptomatic if esophageal luminal clearance is normal but if esophageal peristalsis is defective → delayed clearance of acid → prolonged exposure of mucosa to HCl, pepsin and bile → mucosal damage.
- Symptoms: heart burn (mainly).
- Complications: dysphagia, esophagitis, ulcer, bleeding, stricture & cancer.
- Nonesophageal complications : cough ,asthma , laryngitis & chest pain.

Therapeutic Goals

- Symptomatic relief - healing of esophagitis - prevention of complications.
- Acid suppression is the most effective means of symptom relief and healing of esophagitis, but does not cure the disease. So there is high relapse rate.

Lines of Treatment of GERD

A. Life-Style Modification (delays or prevents recurrence)

1. Remaining upright or in a semisitting position for 2 hours after meals.
2. Elevation of head of patient during sleep.
3. **Diet**:
    - ↓ Meal size (large meal → distention of stomach → ↓ pressure gradient between esophagus & stomach → increasing reflux).
    - Food to be avoided: citrus fruits (mucosal irritants) - fried or fatty food, caffeinated drinks, chocolate, peppermint, spices (↓ LES pressure).
4. **Drugs to be avoided**
    - Anticholinergic drugs & tricyclic antidepressants (delay gastric emptying).
    - Nitrates & calcium channel blockers (smooth muscle relaxants).
    - Smoking, alcohol, caffeine.

B. Drug therapy of GERD (Combination Therapy)

1. **Antacids containing alginic acid** (regularly after meals):
    - Alginate forms a floating gel which blocks the reflux & coats esophagus → rapid pain relief.
2. **Acid-suppressive agents**:
    - PPIs (the main & most effective treatment).
    - H_2 antagonists are backup drugs. A night dose may be combined with PPIs to cover nocturnal breakthrough in HCl release.
    - Recurrence rate is very high thus usually combined with prokinetics.
3. **Prokinetics** (promotility agents), e.g. metoclopramide & domperidone:
    - Increase gastric motility and emptying.
    - Improve LES tone & esophageal motility → ↓ reflux & ↑luminal clearance.
4. **Eukinetic drugs**: inhibit transient lower esophageal sphincter relaxations
    - Baclofen (GABA-B agonist).

DRUG THERAPY OF VOMITING

- Vomiting may occur due to a variety of conditions, e.g. motion sickness, pregnancy, drugs, radiation, GIT disorders, myocardial infarction, hepatitis.

Pathophysiology of vomiting (see figure on next page)

- The brainstem **vomiting center** is located in the medulla. It is rich in muscarinic, histamine H_1 and serotonin 5-HT_3 receptors.
- Efferent impulses from this center coordinate movements of abdominal skeletal muscles and smooth muscles of the stomach → vomiting.
- The vomiting center responds to afferent impulses from:
  1. **Chemoreceptor trigger zone** (CTZ):
     - Responds to chemicals in blood (drugs, toxins, and uremia) or radiation therapy.
     - It is rich in D_2, 5-HT_3, opioid and neurokinin-1 receptors.
  2. **Vestibular system**:
     - It is important in motion sickness.
     - It is rich in muscarinic and histamine H_1 receptors.
  3. **Viscera** (GIT disorders, hepatitis and myocardial infarction):
     - The vagal afferents in the GIT mucosa are rich in 5-HT_3 receptors. Irritation of gastrointestinal mucosa (e.g. by chemotherapy, radiation therapy, ...) causes release of mucosal serotonin and activation of the 5-HT_3 receptors which stimulate vagal afferent impulses to the vomiting center and CTZ.
  4. **Higher centers**
     - Responsible for psychogenic & anticipatory vomiting due to emotions, pain, sights & smells.

The CTZ is outside the BBB thus is accessible to drugs

Antiemetic Drugs

Antiemetic drugs act by inhibiting inputs to vomiting center:

1. **D_2 antagonists:** - metoclopramide – domperidone - promethazine[16]

2. **5-HT_3 receptor antagonists[17]:** e.g. ondansetron,

3. **Antihistamines:** e.g. diphenhydramine, dimehydrinate, meclizine.

4. **Anticholinergics:** e.g. hyoscine.

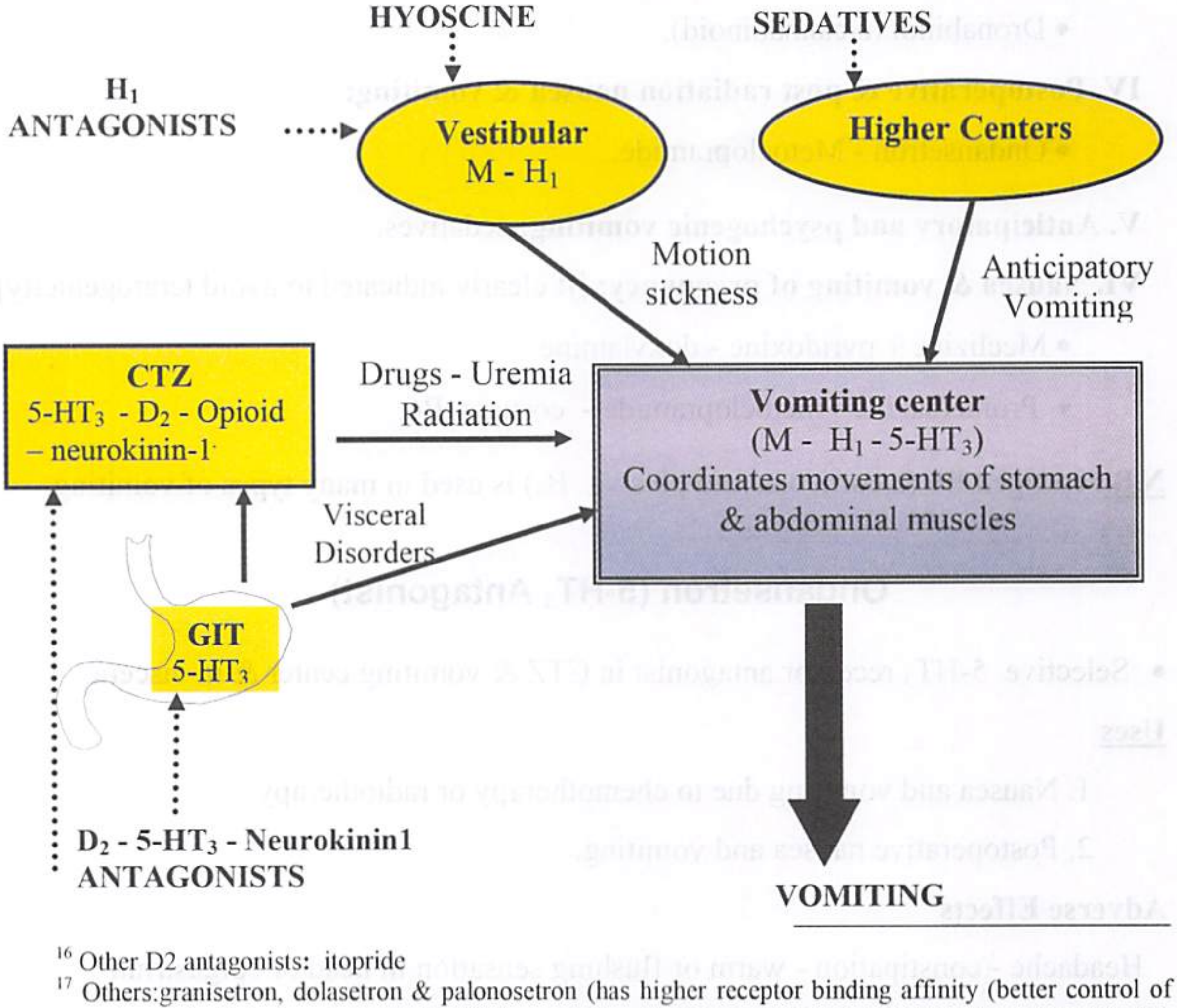
5. **Neurokinin-1 receptor antagonists**: e.g. aprepitant

6- **Sedatives:** benzodiazepines e.g. lorazepam and diazepam.

N.B.: - Corticosteroids are potent antiemetics, with unknown mechanism.

- Dronabinol is a cannabinoid acting on opioid receptors in CTZ.

Receptors Involved in Vomiting Reflex & Site of Action of Antiemetics


HYOSCINE
SEDATIVES
H1 ANTAGONISTS
Vestibular
M - H1
Higher Centers
Motion sickness
Anticipatory Vomiting
CTZ
5-HT3 - D2 - Opioid – neurokinin-1
Drugs - Uremia
Radiation
Vomiting center
(M - H1 - 5-HT3)
Coordinates movements of stomach & abdominal muscles
Visceral Disorders
GIT
5-HT3
D2 - 5-HT3 - Neurokinin1 ANTAGONISTS
VOMITING

---

[16] Other D2 antagonists: itopride

[17] Others:granisetron, dolasetron & palonosetron (has higher receptor binding affinity (better control of acute cytotoxic-induced emesis (CIE) & longer $t_{1/2}$ (better control of delayed CIE). Repeated dosing within 7days is not recommended.

Choice of Antiemetics (depends on the cause of vomiting)

I. Vomiting due to motion sickness (prophylactically better than curatively).

- H1 antagonists: e.g. diphenhydramine, dimehydrinate, meclizine.
- Antimuscarinics: e.g. hyoscine (transdermal patch is better tolerated).

II. Vomiting due to drugs, toxins and uremia:

- D_2 receptor antagonists e.g. metoclopramide and domperidone.

III. Vomiting due to cytotoxics (combinations of antiemetics are used)

- 5-HT_3 antagonists: ondansetron (1st choice, prophylaxis & treatment).
- Corticosteroids potentiate ondansetron.
- DA antagonists: domperidone & metoclopramide.
- Neurokinin-1 antagonists: aprepitant.
- Sedatives (prior to cytotoxics to avoid anticipatory vomiting).
- Dronabinol (a cannabinoid).

IV. Postoperative & post radiation nausea & vomiting:

- Ondansetron - Metoclopramide.

V. Anticipatory and psychogenic vomiting: sedatives.

VI. Nausea & vomiting of pregnancy: [if clearly indicated to avoid teratogenicity]

- Meclizine + pyridoxine - doxylamine.
- Promethazine - metoclopramide - cortigen B6.

N.B.: cortigen B6 (a corticosteroid plus vit. B_6) is used in many types of vomiting.

Ondansetron (5-HT_3 Antagonist)

- Selective 5-HT_3 receptor antagonist in CTZ & vomiting center & in viscera.

Uses

1. Nausea and vomiting due to chemotherapy or radiotherapy.
2. Postoperative nausea and vomiting.

Adverse Effects

Headache - constipation - warm or flushing sensation in head or epigastrium.

Metoclopramide

- Most widely used antiemetic & prokinetic drug acting centrally & peripherally.

Mechanism of Action & Uses

Antiemetic

Central

D_2 antagonist in CTZ

Uses

- Most causes of vomiting except motion sickness:
  - Drug- induced.
  - Uremia or toxin- induced.
  - Radiation - induced.
  - Postoperative vomiting.
  - Vomiting in GIT disorders.

Prokinetic

Peripheral

D_2 antagonist & Cholinomimetic

Promotes gastric emptying by:

- ↑ Gastric motility & esophageal peristalsis.
- ↑ Tone of LES - relaxes pyloric antrum.

Uses

- GERD.
- Gastric atony (delayed gastric emptying & diabetic gastroparesis).
- Endoscopy: facilitates GIT intubation.
- GIT radiology (barium meal).
- Acute migraine attack: to accelerate gastric emptying & facilitate absorption of analgesics.

Adverse effects

1. **Central D_2 antagonist effects**
   - Drowsiness & nervousness (common).
   - Extrapyramidal adverse reactions (dystonia, parkinsonism…).
   - ↑Prolactin, menstrual disturbances, galactorrhea, gynecomastia, impotence.
2. **Peripheral prokinetic effect**: diarrhea.

Domperidone (antiemetic & prokinetic)

- Similar to metoclopramide; less extrapyramidal effects (does not readily cross BBB).

DRUG THERAPY OF DIARRHEA

- Diarrhea involves both an increase in the motility of GIT and a decrease in the absorption of fluid resulting in loss of electrolytes and water.
- Diarrhea can be caused by infectious agents, toxins, food, anxiety or drugs.
- It ranges from mild cases to a major cause of death & malnutrition in children.

Pathophysiology of diarrhoea:

- **Osmotic diarrhea**: due to saline purgatives or carbohydrate malabsorption
- **Secretory diarrhea**: due to exudation into GIT e.g. laxative abuse or bacterial toxins as vibrio cholera & E. Coli.
- **Motility diarrhea**: due to disordered intestinal motility e.g. prokinetic drugs, autonomic neuropathy or hyperthyroidism.
- **Fatty diarrhea**: due to malabsorption syndrome secondary to mineral oil or bile salts/pancreatic secretion deficiency.

Lines of Management

1. Oral rehydration solution (ORS)[18] in conscious patients, IV fluids in severe cases (to correct fluid & electrolyte balance, more important than drugs).
2. Diet: avoid fat, milk, high fiber food.
3. Frequent fluid intake & tea (astringent, precipitates surface proteins).
4. Specific antimicrobial therapy against causative organisms:
    - Floroquinolones for most bacteria except clostridium difficile
    - Metronidazole for clostridium difficile, amoebiasis & giardiasis .
5. Symptomatic treatment: **antidiarrheal agents**.

---

[18] In many small bowel diarrheal illnesses, intestinal glucose absorption via sodium-glucose co-transport remains intact. Thus, the intestine remains able to absorb water if glucose and salt are also present to assist in the transport of water from the intestinal lumen.

ANTIDIARRHEAL AGENTS

I. Antimotility Agents: diphenoxylate, loperamide (opioid- related)

Mechanism of Action

- Act on presynaptic opioid receptors in intestinal mucosa[19] → ↓ ACh release → ↓ peristalsis allowing water and salt to be absorbed back into the body.
- Spasmogenic effect (↑ smooth muscle tone)with diphenoxylate.

Atropine is combined with diphenoxylate to:

1. Relieve its spasmogenic effect.
2. Discourage abuse (which may occur with prolonged use).
3. May contribute to the antidiarrheal action.

Advantages

- At therapeutic doses they do not cross BBB (act only peripherally).
- Loperamide is the least to cross BBB → much lower abuse potential.

Uses

1. In mild to moderate acute diarrhea.
2. To control chronic diarrhea e.g. in irritable bowel syndrome (loperamide).

Overdose Toxicity (with diphenoxylate)

- CNS and respiratory depression.
- Paralytic ileus.

Contraindications

1. Severe colitis, bloody diarrhea, fever & systemic infection as they ↓ GIT motility and lead to retention of toxins → toxic megacolon.
2. Acute gastroenteritis in infants and children (→ paralytic ileus & respiratory depression).

---

[19] Submucosal & myenteric plexus.

II. Drugs increasing stool viscosity (less effective)

a. Adsorbents (pectin, kaolin,)

- Provide protective coat on intestinal mucosa.
- Adsorb toxic substances , bacteria & fluid →↓stool liquidity .
- May interfere with absorption of other drugs.

b. Bulk forming

- Methylcellulose →↓stool liquidity

III. Colloidal bismuth compounds

- Widely used in acute non-specific diarrhea.
- Bismuth subsalicylate is also used in Traveler's diarrhea (due to E. coli):
  - a. Bismuth → direct antimicrobial effect and binds enterotoxins.
  - b. Salicylate content →↓PG synthesis →↓ fluid secretion in bowel.

DRUG THERAPY OF CONSTIPATION

- Anti-constipation drugs are used to treat constipation by enhancing colonic transit.

Classification According to Mechanisms of Action

1. Bulk Laxatives

Indigestable fibers that are unabsorbed in GIT → adsorb H_2O forming a bulky emollient gel → distend colon & stimulate peristalsis.

- Bran - Psyllium
- Methyl cellulose

2. Osmotic Laxatives

Non absorbable salts or sugars that hold water by osmotic force → ↑ stool fluidity & intestinal distension → stimulate peristalsis.

- $MgSO_4$ - MgO (milk of magnesia).
- Lactulose.
- Sorbitol.
- Polyethylene glycol solution (PEG).

3. Stool Lubricants

Paraffin oil

- ↓ Water absorption from stools → lubricates hard stool.

4. Stool softeners

Soften hard stools → easy passage.

- **Evacuant enema & glycerin suppository**: ↑ water content of stools.
- **Docusate:** ↑ water entry into stools by decreasing its surface tension.

5. Stimulants/ Irritants

They irritate the colon → stimulate peristalsis chemically

- **Castor oil** → hydrolyzed to ricinoleic acid → stimulates small intestinal peristalsis → potent fast effect.
- **Bisacodyl** → stimulates colonic peristalsis → mild delayed effect.
- **Anthraquinones** (cascara - senna – aloes) → release emodin → absorbed from the small intestine → enters the enterohepatic circulation to be excreted in the colon (delayed onset: 6-8 h).

Types of anti-constipation drugs

Laxatives: mild effect → well formed stool (e.g. bran)

Purgatives: moderate effect → loose stool (e.g. lactulose)

Cathartics: strong effect → watery stool (e.g. magnesium sulphate)

Uses

1. Constipation[20] (unless contraindicated):
   i. Intermittent constipation → is best treated by high fiber diet, plenty of fluids & exercise.
   i. Constipation with low bulk stool → bulk- forming or osmotic agents.
   iii. Constipation with low frequency of defecation → stimulant agents.
   iv. Constipation with hard stool → stool softeners.
   v. Constipation with impacted stool→ lubricants (parrafin oil)
2. After anal surgery→ lubricants (parrafin oil).
3. Colonic preparation → castor oil, bisacodyl & PEG solution are given before surgery, colonoscopy & abdominal x-ray to clean the colon.
4. Hepatic encephalopathy → lactulose.
5. Ingested poison & taenia solium treatment → $MgSO_4$.
6. Irritable bowel syndrome.
7. Obesity.
8. Gall stones

} Bulk – forming agents plus large amount of fluids

General Adverse Effects

1. Cathartic habit and atonic colon[21].
2. Abdominal cramps.
3. Diarrhea, dehydration and hypokalemia.
4. Abortion and excretion in milk during lactation.

---

[20] Castor oil should not be taken at night due to its rapid effect while bisacodyl should be taken at night since its action is delayed for 6 hours.

[21] Cathartic colon is due to degeneration of Aeurbach's plexus.& loss of normal defecation mechanism. The colon is distended with stool till it contracts by its myogenic property with evacuation of large volume of stool.

Special Adverse Effects

Bulk – forming agents

- Hard stools & intestinal obstruction if not taken with plenty of fluids.
- Bloating & flatus (due to bacterial digestion of the plant fiber).
- ↓ Absorption of iron (anemia), Ca^{2+} (osteoporosis) and fat (steatorrhea).

Paraffin oil

- Decreases absorption of fats (steatorrhoea) and fat-soluble vitamins.
- Leakage causing eczema around anus- bowel lymph node granulomata.
- Lipid pneumonia[22].

Senna

- Mutagenic.

Docusate

- Intestinal obstruction.

Bisacodyl

- Purple coloration of urine[23].

Lactulose

- Flatulence - abdominal colic – diarrhea.
- Aggravates diabetes.

Contraindications

1. Undiagnosed acute abdomen (e.g. appendicitis).
2. Intestinal obstruction (→ rupture).
3. Hemorrhoids.
4. Pregnancy (→ abortion)

---

[22] Lipid pneumonia occurs due to back leakage of paraffin into the oesophagus when the patient lies down during sleep → enters the lung

[23] This occurs in alkaline urine. Phenolphthalein; another ingredient usually present in most OTC laxatives turns urine pink. These can be used as bedside test to diagnose suspected laxative use (e.g. in hypokalaemic patients)

IRRITABLE BOWEL SYNDROME

- Irritable bowel syndrome (IBS) is a chronic relapsing disorder occurring in 80 % of adults. It is characterized by abdominal distension, pain, diarrhea, constipation or both. It is associated with anxiety or depression.

Management

1. Diet

- Small frequent meals to avoid gas distension.
- Diet rich in soluble fibers.
- Reduce insoluble fibers (bran, raw fibrous vegetables, unpeeled fruits).
- Avoid flatulogenic foods: beans, cabbage, cauliflower, legumes, onion, eggs, lentils, grapes, caffeine & carbonated drinks.

2. Improvement of bowel disturbance

- Patients with predominant diarrhea: loperamide – diphenoxylate.
- Patients with predominant constipation:
  - ↑ Fiber content of diet.
  - Bulk laxatives e.g. psyllium (but may ↑ gas production & bloating).
  - Osmotic laxatives (MgO or lactulose) .

3. Relief of abdominal discomfort and pain

- Anticholinergics & direct smooth muscle relaxants.
- Antiflatulent drugs (simethicone & charcoal): for gas distension.
- 5HT3 receptors antagonists (alosetron): for diarrhea- predominant IBS
  - Modulates visceral afferent pain sensation & intestinal motility - ↓Central response to visceral stimulation (side effect: constipation - ischemic colitis).
- 5HT4 receptors agonists (tegaserod): for constipation-predominant IBS
  - Stimulates peristalsis by its prokinetic effect (side effect: diarrhea)
- Kappa receptor agonists (trimebutine): for pain-predominant IBS.

4. **Unabsorbable antibiotics**: for enteric pathogenes e.g., rifaximine

5. **Relief of depression and anxiety**: antidepressants & anxiolytics.

HEPATIC ENCEPHALOPATHY

(Defective brain functions 2^{ry} to liver cell failure)

Hepatic encephalopathy is characterized by disturbance in consciousness and behavior resulting from an increase in brain ammonia and other toxins due to failure of the liver to detoxify them. It is aggravated by:

- Excess NH_3 (hypokalemia - excess dietary protein - GIT bleeding).
- Infection and hypoglycemia: may disturb brain function.

Treatment

1. Treatment of precipitating factors: infection, GIT bleeding, hypokalemia or hypoglycemia.
2. H_2 Antagonists: decrease acidity, gastric erosions and bleeding.
3. Drugs decreasing portal pressure: ↓ bleeding of esophageal varices:
    - Octreotide - vasopressin (plus nitrates) - β Blockers
4. Decrease ammonia by:
    - Decrease dietary protein.
    - Evacuant enema with lactulose .
    - **Lactulose** (mainstay of therapy, see below)
    - Neomycin (kills bacterial flora which form ammonia from proteins).
    - Probiotics e.g. Lactobacillus → displacement of urease-containing bacteria.
    - Stimulation of ammonia metabolism:
        i. Ornithine-aspartate: increase ammonia removal by hepatocytes via stimulation of glutamine synthesis.
        ii. Sodium benzoate
5. Flumazenil: benzodiazepine receptor antagonist[24]

---

[24] The GABA-receptor complex is activated in hepatic encephalopathy possibly through ↑ endogenous benzodiazepine receptor ligands.

Lactulose

Mechanism

A nonabsorbable synthetic disaccharide digested by colonic bacterial flora into short chain organic acids → acidifies colon contents leading to:

- Binding of ammonia.
- Inhibition of ammonia producing bacterial flora.
- Osmotic laxative effect.

Uses

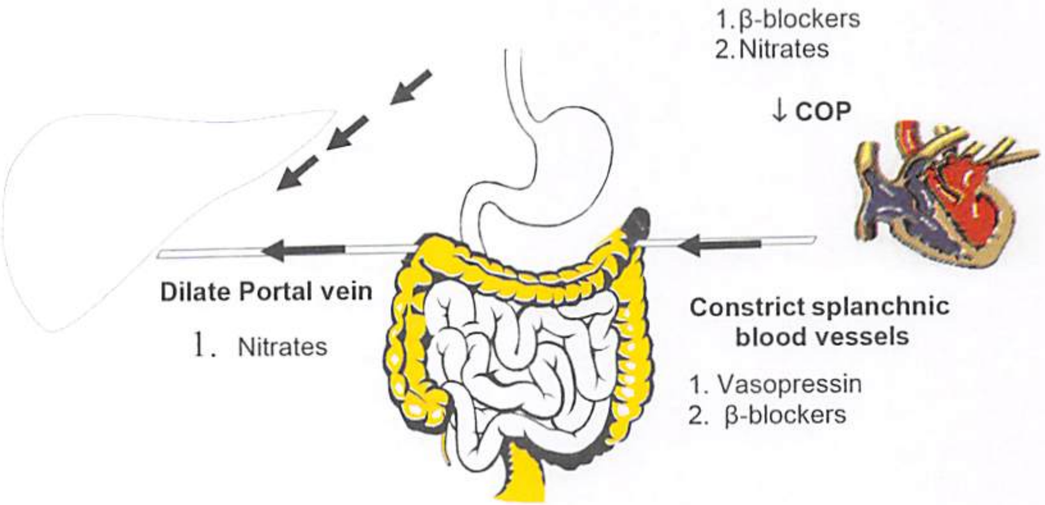
1. Hepatic encephalopathy.
2. Constipation.

Adverse Effects

1. Flatulence.
2. Abdominal colic.
3. Diarrhea.
4. Aggravates diabetes

DRUG THERAPY OF ESOPHAGEAL VARICES

(Dilated lower esophageal veins)


1. β-blockers
2. Nitrates
↓ COP
Dilate Portal vein
1. Nitrates
Constrict splanchnic blood vessels
1. Vasopressin
2. β-blockers

Control of Bleeding Varices

1. **IV vasopressin or** terlipressin[25]

   Constrict mesenteric blood vessels →↓ portal blood flow.

2. **IV vasopressin combined with IV nitroglycerin** (↓systemic vasoconstriction induced by vasopressin & accentuates its portal hypotensive actions.

3. **Octreotide**:
   - Direct vasoconstrictor of splanchnic arterioles.
   - Inhibits release of peptides contributing to hyperdynamic circulation in portal hypertension.

4. **IV ranitidine:** immediately after control to prevent re-bleeding.

Prophylaxis of variceal bleeding in patients with cirrhosis[26]

- **Non-selective β blockers** (e.g. propranolol and nadolol) →

  i. Block adrenergic VD tone in mesenteric arterioles → unopposed α VC →↓ portal inflow.

  ii. ↓Cardiac output(COP).

---

[25] Vasopressin analog released in a slow & sustained manner at vascular smooth muscle.

[26] Prophylaxis with isosorbide mononitrate → ↑mortality in patients > 50 years.

Lecture Notes

PHARMACOLOGY

Volume 3

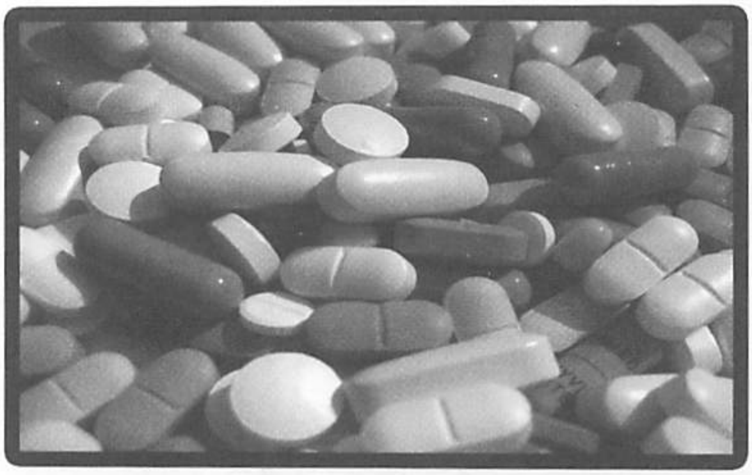
- Endocrine
- Chemotherapy & Immunotherapy
- NSAIDs & CNS

Pharmacology Department
Faculty of Medicine
Ain Shams University
2019/2020

Lecture Notes
PHARMACOLOGY

Volume 3

- Endocrine
- Chemotherapy & Immunotherapy
- NSAIDs & CNS



Pharmacology Department
Faculty of Medicine
Ain Shams University
2019/2020

Preface

Pharmacology is an ever-changing medical science. The recent, rapid advances in molecular biology and biotechnology have added relevant information to drug therapy. This edition of "Lecture Notes on Pharmacology" provides the most recent advances in drug therapy within a concise framework.

This work is the result of the combined effort of the Professors of Pharmacology Department; Ain Shams University. "Each of us is unique in their own way. We have something to learn from everyone". Colleagues and students are encouraged to communicate their suggestions. Authors will be pleased to receive comments concerning this edition

Head of Pharmacology Department

Professor Dr. Lobna Bassyouni

2019-2020

Professors of Pharmacology Department

Head of Department

Prof. Dr. Lobna Bassyouni

Prof. Dr. Ahmed Nour Eldin
Prof. Dr. Sahar Kamal

Editorial Board: Prof. Dr. Ahmed Abdel-Salam - Prof. Dr. Olfat Hassan

Authors

Prof. Dr. Zeinab Labib
Prof. Dr. Ahmed Abdel-Salam
Prof. Dr. Olfat Hassan

Prof. Dr. Hoda Sallam
Prof. Dr. Mona Hassan
Prof. Dr. Dr. Sonia Saleeb
Prof. Dr. Osama El Serafy
Prof. Dr. Ahmed Khalil

Prof. Dr. Mohamed Abdel-Bary
Prof. Dr. Ahmed Abedel Tawab
Prof. Dr. Sawsan Abou el Fetouh
Prof. Dr. May Hamza
Ass Prof. Amany Helmy

Deep appreciation for the valuable contribution of

Prof. Dr. Yousria Wahba
Prof. Dr. Samira Mahmoud
Prof. Dr. Adel el Bakry
Prof. Dr. Mahdy Salama

Prof. Dr Sayed Kamel
Prof. Dr. Somia Massoud
Prof. Dr Atef EL-Esawy.
Prof. Dr. Ahmed Badawy

Computer graphics & designs: Dr. Essam Ghazaly - Dr. Mohamed Bahr

CONTENTS

Volume III

1. Endocrine Pharmacology ....9 - 62

2. Chemotherapy ....65 - 132

3. Immunopharmacology...135 - 148

4. NSAIDs & Gout therapy 151- 164

5. CNS Pharmacology 167- 237

I. ENDOCRINE PHARMACOLOGY

Intended Learning Outcomes (ILOs)

By the end of this chapter, the student should be able to recognize the following ILOs

Hypothalamic & pituitary hormones: the student should be able to

- Identify the uses of octreotide.
- Compare between different routes of administration of GnRH and their clinical implications.
- List the uses of bromocriptine.
- Identify drugs used in acromegaly.
- Compare between the use of cosyntropin and gluccorticoids.
- Discuss the effects of vasopressin and its analogs on vascular smooth muscle and the kidney.
- Recognize the adverse effects of vasopressin and its analogs.

Antidiabetic Drugs: the student should be able to

- Compare between different preparations of insulin.
- Describe the mechanisms of action of oral antidiabetics.
- Compare between the different anidiabetic drugs regarding their tendency to induce hypoglycemic effects & weight gain.
- Explain why in severe renal or liver diseases, insulin & not oral antidiabetics must be used.
- Explain why during stress & in pregnancy & lactation, insulin & not oral antidiabetics must be used.
- Explain why metformin is contraindicated in renal & liver failure & in severe hypoxia.
- Recognize that rosiglitazone may induc heart failure.
- Describe the strategies for managing of type 1 & type 2 diabetes.
- Recognize that metformin is recommended for initial management of type 2 DM & recall its advantages.
- Discuss when & why 5% glucose, K^+ & HCO_3 are administred in ketoacidosis.

Drugs & Bone Calcium Homeostasis: the student should be able to

- Review the regulation of calcium homeostasis and the physiological actions of parathyroid hormone, calcitonin and vitamin D.
- Discuss the beneficial effects of drugs used in osteoporosis.
- List drugs that lower blood calcium in hypercalcemia.
- List 2 Vitamin D preparations suitable for patients with poor renal function.
- Explain why alendronate is taken while sitting & with a full glass of water.
- Discuss the clinical significance of the anti-vitamin D effect of corticosteroids.

Antithyroid Drugs: the student should be able to

- Recognize the 3 possible options (thionamide therapy, radioactive iodine or surgery) for management of thyrotoxicosis & discuss the basis for choice between these options in different cases. Recognize that thionamides must still be given in all cases.
- Outline the steps of synthesis & release of T3 &T4 & the site of action of antithyroid drugs.
- Explain the rationale for the use of propranolol in treatment of hyperthyroidism.
- List the indications of iodide salts in thyrotoxicosis & explain why they are not used in long term therapy.
- List the most common adverse effect of thionamides &the most serious one.
- Explain why methimazole is preferred to propylthiouracil for treating hyperthyroidism.
- Explain why propylthiouracil is preferred to methimazole during pregnancy.
- List 3 beneficial effects of hydrocortisone in thyrotoxic crisis.

Corticosteroids: the student should be able to

- Recognize the adverse effects of corticosteroids as an extension of their widespread pharmacological actions.
- Discuss the different precautions required during therapy with corticosteroids.
- Compare between different preparations of corticosteroids versus the natural hormone.
- Recognize the widespread use of corticosteroids &the choices of different preparations.
- List the inhalation corticosteroid preparations and their advantages.
- Explain why steroids are used in stress, cerebral edema & hypercalcemia.

Sex Hormones: the student should be able to

- Discuss the types and mechanism of action of contraceptives.
- Explain why progetins are added to estrogen in contraceptive pills.
- Recall the adverse effects of oral cotraceptives. Recognize that most are due to estrogen. List those induced by progestins.
- Describe the differrent mechanisms of drugs used in female infertility.
- Discuss how the difference in site of action of clomiphene and tamoxifen results in differences in their therapeutic uses.
- Compare the effects of estrogen receptor modulators & estrogen on bone, breat and uterus.
- List the of adverse effects of anabolic steroids.
- Compare the mechanisms of action of finasteride and flutamide and their uses.

ENDOCRINE PHARMACOLOGY

CLINICALLY IMPORTANT HYPOTHALAMIC HORMONES

1. Hormones for diagnostic purposes:

- Growth hormone-releasing hormone: diagnosis of growth hormone deficiency.
- Corticotropin-releasing hormone: to test hypothalamic pituitary function in ACTH deficiency or excess.
- Thyrotropin-releasing hormone: diagnosis of mild hyper or hypothyroidism.

2. Gonadotropin-Releasing Hormone (GnRH)

- **Gonadorelin** (Synthetic).
- **Leuprolide & nafarelin** (GnRH analogs).

Uses:

1. Given in SC pulses to ↑ gonadotropins to stimulate ovulation in infertility.
2. Given continuously[1] to inhibit gonadotropins release in: cancer prostate - endometriosis (inhibit ectopic menstruation) - in-vitro fertilization.

   N.B.: In "***in-vitro*** fertilization" endogenous gonadotropin release is inhibited & exogenous FSH is given to induce follicular maturation at a selected time.

Adverse effects:

- Headache – hot flushes-depression
- Vaginal dryness- decreased libido- ovarian cyst.
- Osteoporosis.

Contraindications: pregnancy –lactation

GnRH antagonists: ganirelix- degarelix

Uses:

- Controlled ovarian hyper-stimulation (inhibit LH surge).
- Advanced prostatic cancer.

---

[1] Continuous administration → tachyphylaxis due to down regulation of pituitary receptors.

3. Growth Hormone-Inhibiting Hormone (Somatostatin)

- It Inhibits release of growth hormone, GIT hormones, insulin & glucagon.
- Its short $t_{½}$ (1-3 min) & non-specificity (inhibits other secretions) limit its use.

Octreotide: long-acting somatostatin analog ($t_{½}$ 80 min → preferred).

Uses (given sc)

1. GIT tumors secreting VIP – gastrinomas –glucagonomas.
2. Bleeding esophageal varices (of choice; see GIT)
3. Carcinoid syndrome.
4. Acromegaly.

Adverse effects

- Nausea -vomiting –abdominal cramps- gall stones.
- Pain at site of injection.
- Vitamin B12 deficiency.

4. Prolactin-Inhibiting Hormone (= Dopamine)

Bromocriptine

- Orally active DA agonist
- Inhibits prolactin secretion.
- ↑growth hormone secretion (in normal) but paradoxically inhibits it in acromegaly.

Uses

1. Prolactin-secreting adenomas.
2. To stimulate ovulation in infertility due to hyperprolactinemia.
3. Amenorrhea & galactorrhea in hyperprolactinemia.
4. To prevent breast engorgement (suppresses physiologic lactation).
5. Parkinsonism (orally active DA agonist).
6. Acromegaly: ↓ GH secretion.

Drugs used in Acromegaly

Octreotide - Bromocriptine – L-dopa

Adverse effects:

- Nausea- orthostatic hypotension - confusion.

N.B.: other DA agonists; cabergoline (long half-life; given twice/week).

CLINICALLY IMPORTANT PITUITARY HORMONES

A. Anterior Pituitary Hormones

1. Growth Hormone (GH):

Somatropin : recombinant human growth hormone

Uses:

- Promotes growth in growth hormone deficiency.

Side effects:

- Hyperglycemia.
- Edema-myalgia.
- Enzyme inducer.

2. Thyroid-Stimulating Hormone (TSH)

Therapeutic Uses

1. Diagnostic: differentiates between 1^{ry} and 2^{ry} Hypothyroidism.
2. Adjuvant to I^{131} therapy in metastatic thyroid carcinoma.

3. Andrenocorticotrophic Hormone (ACTH)

- Stimulates adrenal cortex to release glucocorticoids (mainly) & androgens.

Cosyntropin:

- Synthetic ACTH developed to avoid ACTH-induced allergy.

Therapeutic Uses

1. Diagnostic (mainly): in patients with abnormal corticosteroid production.
2. Anti-inflammatory & immunosuppressive in chronic conditions (glucocorticoids are preferred since cosyntropin is given by injection & its mineralocorticoid activity can not be separated from its glucocorticoid effects).

4. Gonadotropins FSH, LH

- Stimulate spermatogenesis & testosterone secretion in males.
- Stimulate ovulation & ovarian estrogen & progesterone production in females.

Clinically Used Gonadotropins

1. **Human Menopausal Gonadotropins** (hMG)[2]:
   - Menotropins (FSH + LH).
   - Urofollitropin (FSH)., recombinant FSH (r-FSH).
2. **Human Chorionic Gonadotropins** (hCG)[3]: Similar to LH.

Therapeutic Uses (parentral)

1. Infertility (♂ & ♀) - in vitro fertilization.
2. Undescended testis.
3. 1^{ry} or 2^{ry} amenorrhea due to lack of gonadotropins.

Adverse Effects

1. Hyperstimulation syndrome: enlarged ovary - ascites – hemoperitoneum.
2. Multiple births.
3. Spontaneous abortions.
4. Gynecomastia in males.

---

[2] Extracted from urine of post menopausal females.

[3] Produced by human placenta & excreted in urine.

B. Posterior Pituitary Hormones

1. Vasopressin "Antidiuretic Hormone (ADH)"

- ADH acts on vascular (V_1) & renal & extrarenal (V_2) receptors.

ADH analogues

1. V_1 Selective

Terlipressin – Felypressin.

2. V_2 Selective

Desmopressin.

V_1 Receptors

Vascular

(Vasoconstriction)

- Large doses of ADH, act on vascular V_1 receptors → vasoconstriction → ↑ BP.

Uses

1. Bleeding in esophageal varices & during surgery in portal hypertension.
   (↑↑ splanchnic VC)

   Terlipressin

   (Preferred to ADH)

   - Longer acting
   - Less side effects
2. Prolong the action of local anesthetics.

   Felypressin

   ☐ Safer than epinephrine in cardiac patients.

V_2 Receptors

Renal

(Antidiuresis)

- ADH acts on renal V_2 receptors → ↑ reabsorption of H_2O in collecting ducts.

Use

ADH-sensitive Diabetes Insipidus.

Vasopressin

☐ Weak V_2 selectivity.

☐ Short-acting.

☐ Given SC or IM.

Desmopressin

Preferred to ADH:

☐ V_2 selective: → more potent antidiuretic, minimal VC.

☐ Long-acting.

☐ Given intra-nasally.

V_2 Receptors

Extrarenal

(↑ clotting factors)

- ADH → ↑ release of factor VIII & von Willebrand factor.

Uses

1. Haemophilia A.
2. Von Willebrand disease.

Desmopressin

Adverse Effects

1. Vasoconstriction: marked facial pallor - coronary spasm - ↑ BP.
2. Colic.
3. Allergic reactions.
4. Water intoxication: avoid drugs potentiating its effect:
    - ☐ Carbamazepine: sensitizes renal tubules to ADH.

Vasopressin (ADH) antagonists

- Increased ADH secretion resulting in water retention & hyponatremia occurs in:
    1. Syndrome of inappropriate secretion of ADH (SIADH) e.g., in lung cancers, head injuries.
    2. CHF
- **ADH antagonists that may be used in such conditions include**:
    1. Demeclocycline (used in SIADH, largely replaced lithium).
    2. Vaptans (used in SIADH, CHF with hyponatremia):
        - i. Conivaptan: nonselective V_1& V_2 antagonist, given IV.
        - ii. Tolvaptan: selective V_2 antagonist, given orally.

        Adverse effects:

        - Polyuria.
        - Thirst.
        - Hypernatremia.
        - Infusion site reactions.

2. Oxytocin

Actions

1. Breast: contraction of myoepithelial cells lining ducts of the breast → squeezing milk out of lactating breast (milk ejection).
2. Uterus: contraction of smooth muscles of the uterus.
3. Induction and maintenance of labor.

Therapeutic Uses of Syntocinon (Synthetic Oxytocin)

1. Induction of labor: uterine enertia, incomplete abortion; IV.
2. Postpartum hemorrhage; IM (but ergometrine is preferred).
3. Impaired milk ejection; nasal spray.

Toxicity

1. Uterine rupture.
2. Fetal asphyxia.
3. Water retention and intoxication.

Oxytocin antagonist : Atosiban

Uses:

- Premature labor (iv infusion).

INSULIN & ORAL ANTIDIABETIC DRUGS

Hormones Secreted by Islets of Langerhans[4]

Insulin	Glucagon	Somatostatin
Secreted by β cells (During feeding) • Anabolic hormone → storage of glucose, amino-acids & fatty acids.	Secreted by α cells (During fasting) • Mobilizes stored glucose, NH_2 acids & fatty acids into blood to maintain blood glucose.	Secreted by δ cells • Inhibits secretion of insulin & glucagon.

N.B.: **Amylin** is produced by β cells. It decreases appetite, slows gastric emptying, reduces inappropriate glucagon secretion and reduces food intake.

INSULIN

- Insulin is a protein consisting of two amino acid chains, alpha (21 aa) and beta (30 aa) connected by two disulfide bridges.
- Insulin is synthesized as a precursor (pro-insulin) which is enzymatically cleaved in β cells into C peptide and mature insulin which are stored in granules & secreted in equimolar amounts. C peptide determination is an estimate of insulin secretion.
- Insulin secretion is regulated mainly by blood glucose levels (and also by other hormones and autonomic mediators).

---

[4] GIT hormones that may modulate glucagon and/or insulin secretions include glucagon-like peptide-1 and ghrelin.

Metabolic Effects of Insulin & Metabolic Disturbances in Diabetes

- Insulin affects carbohydrate, fat & protein metabolism by acting on specific insulin receptors in 3 principle tissues: liver - skeletal muscle -adipose tissue.

I. Effect of Insulin on Carbohydrate Metabolism

- Insulin ↓ blood glucose level by:
  - a. ↑Hepatic glucose storage → ↓ hepatic glucose production (⊕ glycogenesis, ⊖ glycogenolysis & gluconeogenesis).
  - b. ↑ Uptake & storage of glucose in:
    - Skeletal muscle → ⊕ glycolysis → energy production.
      ↘ ⊕ glycogenesis → glycogen storage.
    - Fat cells → ↑ glycerol → TGs synthesis.
- Insulin deficiency in diabetes results in ↑ blood glucose by ↑ glucose production from liver and ↓ glucose uptake by skeletal muscle and fat cells.
- If glucose level exceeds renal threshold → glucosuria→ osmotic diuresis (polyuria) → dehydration → thirst → polydypsia.

II. Effect of Insulin on Fat Metabolism

- Insulin promotes fat storage through:
  - ⊕ Plasma lipoprotein lipase → hydrolysis of TGs from circulating lipoproteins → ↑ free fatty acids (FFAs) supply to adipose tissue.
  - ↑ Glucose uptake in fat → ↑ glycerol which binds FFAs → ↑ TGs.
  - ⊖ Lipolysis (⊖ intracellular lipase) → ↓ FFAs mobilization to blood.
- Insulin deficiency in diabetes results in:
  - ↑ Lipolysis → ↑ free fatty acids in blood.
  - ↑ Breakdown of fat for energy supply → ↑ Acetyl CoA which in absence of aerobic CHO metabolism → ↑ ketone bodies.

III. Effect of Insulin on Protein Metabolism

- Insulin promotes protein storage through:
  - ↓ Protein breakdown in liver - ↑ Protein synthesis in skeletal muscle.
- Insulin deficiency→↑ protein breakdown & ↓ synthesis → muscle wasting.

Mechanism of Action of Insulin

- Insulin acts on a specific receptor[5] consisting of two α and two β subunits.
- α Subunits are extracellular & carry the insulin binding site. The β subunits span the cell membrane, their intracellular end has tyrosine kinase activity.
- Insulin binds to α subunits → tyrosine kinase autophosphorylation → ↑activity of intracellular protein kinases affecting metabolic enzymes as phosphorylase, lipase...

Insulin Counter-regulatory Hormones

- Released during stress → antagonize insulin effects on blood glucose → ↑ insulin requirements:
  - ☐ Glucagon - Catecholamines - Corticosteroids
  - ☐ Growth Hormone - Thyroxine

Diabetes Mellitus

- Diabetes is a disease characterized by chronic hyperglycemia due to an absolute or relative lack of insulin (reduced sensitivity to its action [insulin resistance]).
- **It is diagnosed by:**
  - ☐ Fasting blood sugar (FBS) ≥ 126 (normal < 120 mg/dl).
  - ☐ 2-hours blood sugar after oral 75 g glucose ≥ 200 (normal < 140 mg/dl).
  - ☐ **Glycated hemoglobin** (A1C)
    - ☐ A1C ≥ 6.5% (upper limit in nondiabetic = 6.1%).
    - ☐ Target for therapy according to the American Diabetes Association:< 7%

N.B.: the degree in reduction of A1C gives an idea about efficacy of therapy.

---

[5] Insulin receptor number is increased by exercise, high fiber diet and ↓ body weight.

Types of Diabetes

- **Type 1 DM**
- **Type 2 DM**
- **Other specific types:** e.g. Genetic defects of beta-cell function, diseases of the exocrine pancreas, endocrinopathies[6] or drug or chemical induced.
- **Gestational diabetes mellitus**

Type 1 DM	Type 2 DM
Pathogenesis • Absolute insulin deficiency due to massive β cell destruction. • May be immune mediated or idiopathic.	**Pathogenesis** • Resistance to both endogenous and exogenous insulin commonly accompanied by insufficient insulin release.
• Insulin must be given to control hyperglycemia (insulin dependent).	• It may be adequately treated without exogenous insulin.
• Ketoacidosis is liable to occur.	• Ketoacidosis is rare.

Drugs Inducing Diabetes[7]

1. Glucocorticoids
2. Oral contraceptives

} ↑Insulin resistance by ↓ affinity to receptors

3. Thiazide diuretics (↓ Insulin release).
4. Beta blockers (glucose intolerance)

---

[6] Endocrinopathies include: acromegaly, hyperthyroidism, glucagonoma, somatostatinoma, Cushing's syndrome, pheochromocytoma, aldosteronoma.

[7] Atypical or typical antipsychotic agents may be associated with worsening hyperglycemia. Some of these agents are associated with weight gain, obesity, hypertriglyceridemia, and development of diabetes mellitus, by an as-yet-unidentified mechanism. Monitoring for diabetes is advised in these patients.

Drug therapy of diabetes

Insulin Therapy

Preparations of Human Insulin (biosynthetic " recombinant DNA")

Ultra- rapid **Ultra- short** **Lispro – Aspart - Glulisine**	**Short-Acting** **Regular or Crystalline Zinc**	**Intermediate-Acting** **(NPH)** **(Isophane)**	**Long-Acting**[8] **Glargine**[9]
• Ultra-rapid onset, very short duration. → given SC 15 minutes before meals.	• Rapid onset, short duration → given SC 30-45 min before meals.	• Intermediate onset and duration → given SC 2-4 times /d in type 1 → may be given once/d in type 2 • Variable absorption > 50%	• Slow onset - long acting (broad conc. plateau) → SC once or twice /day
Advantages[10] • Rapid absorption & rapid onset → better postprandial glycemic control. • Very short duration of action → less risk of hypoglycemia.	**Advantages** • Used IV/ IM in emergencies: ketoacidosis....	**Advantages** • Can be mixed with regular insulin[11]. Premixed fixed concentrations are available. • Useful in all forms of diabetes except ketoacidosis.	**Advantages** • Maximum effect maintained for 24 h → ↑ compliance.

Inhaled insulin: **Afrezza** (rapid acting human insulin inhalation powder)

- Covers prandial insulin requirements.
- Type 1 diabetics on afrezza as prandial insulin must also use SC, long-acting insulin.
- **Disadvantages**:
  - Fine dose adjustments are not possible.
  - Not recommended in smokers & contraindicated in cases of chronic lung disease.

---

[8] Insulin detemir is another long acting analogue with a duration of action > 12 h.

[9] Should not be mixed with other types of insulin in same syringe. A new long acting insulin analogue: Degludec may be mixed with rapid-acting insulins without altering the kinetics of Degludec or the rapid-acting insulin.

[10] Available as premixed fixed concentrations with protaminated lispro (NPL) or protaminated aspart (NPA).

[11] Can be mixed with insulin Lispro or Aspart immediately before injection

Indications of Insulin Therapy [Compare with CI of sulfonylureas]

1. Type 1 DM.
2. Type 2 DM.[12]: insulin is added if diet regulation & exercise plus metformin or other oral antidiabetics fail to control hyperglycemia.
3. DM with pregnancy & lactation: To avoid risk of sulfonylurea-induced hypoglycemia in fetus & newborn.
4. DM with stress & emergency: regular insulin is used in diabetic ketoacidosis, surgery, infection, myocardial infarction or severe psychic stress (oral hypoglycemics fail to control hyperglycemia as stress →↑ insulin requirements).
5. DM with severe liver or renal disease: To avoid risk of hypoglycemia by sulfonylurea.
6. Treatment of hyperkalemia: Insulin enhances k^+ influx into cells.

N.B.: Insulin use in pregnancy, lactation, stress, emergency or hyperkalemia is temporary.

Adverse Reactions of Insulin

I. Hypoglycemia

Most frequent
and
most serious

See below

II. ↑ Body Weight

III. Immune Reactions

(Due to anti-insulin antibodies)

A. Insulin resistance:
- Insulin requirements >120 units/d.

B. Allergy:
- Urticaria (rare).

IV. Lipodystrophy

- **Lipohypertrophy**: Due to repeated injection at same site → change site regularly.
- **Lipoatrophy**[13]
Extremely rare.

N.B.: **Hypokalemia** may occur when high doses of insulin are used (e.g. in treatment of ketoacidosis).

---

[12] Insulin may be a 1st -line therapy in type 2 patients with A1C >10 %, fasting plasma glucose >250 mg/dL, random glucose consistently >300 mg/dl, or ketonuria.

[13] Lipoatrophy was formerly seen with animal insulin as it forms immune complexes at injection site.

Insulin-induced Hypoglycemia

- Most frequent adverse effect.
- It can be very serious → brain damage.
- **Causes**: insulin overdose, ↓ food, physical effort.

Warning signs:

- Adrenergic⊕: ↑ HR, sweating, tremors (masked by β-B).
- Neurological signs: Dizziness, convulsions or coma.

Treatment:

- Rapid administration of glucose (sugar or candy).
- IV glucose or glucagon 1 mg IM or SC.

To avoid hypoglycemia, patient should be aware of warning signs & carry few pieces of sugar.

Oral Antidiabetics[14]

I. Insulin Secretagogues

- Sulfonylureas : e.g. glimepiride
- Non-sulfonylureas :e.g. repaglinide

II. Insulin Sensitizers

- **Biguanides:** metformin
- **Thiazolidinediones (Tzd):** pioglitazone

III. α-glucosidase Inhibitors e.g. acarbose

IV. Sodium-glucose co-transporter 2 (SGLT2) inhibitors: e.g. canagliflozin

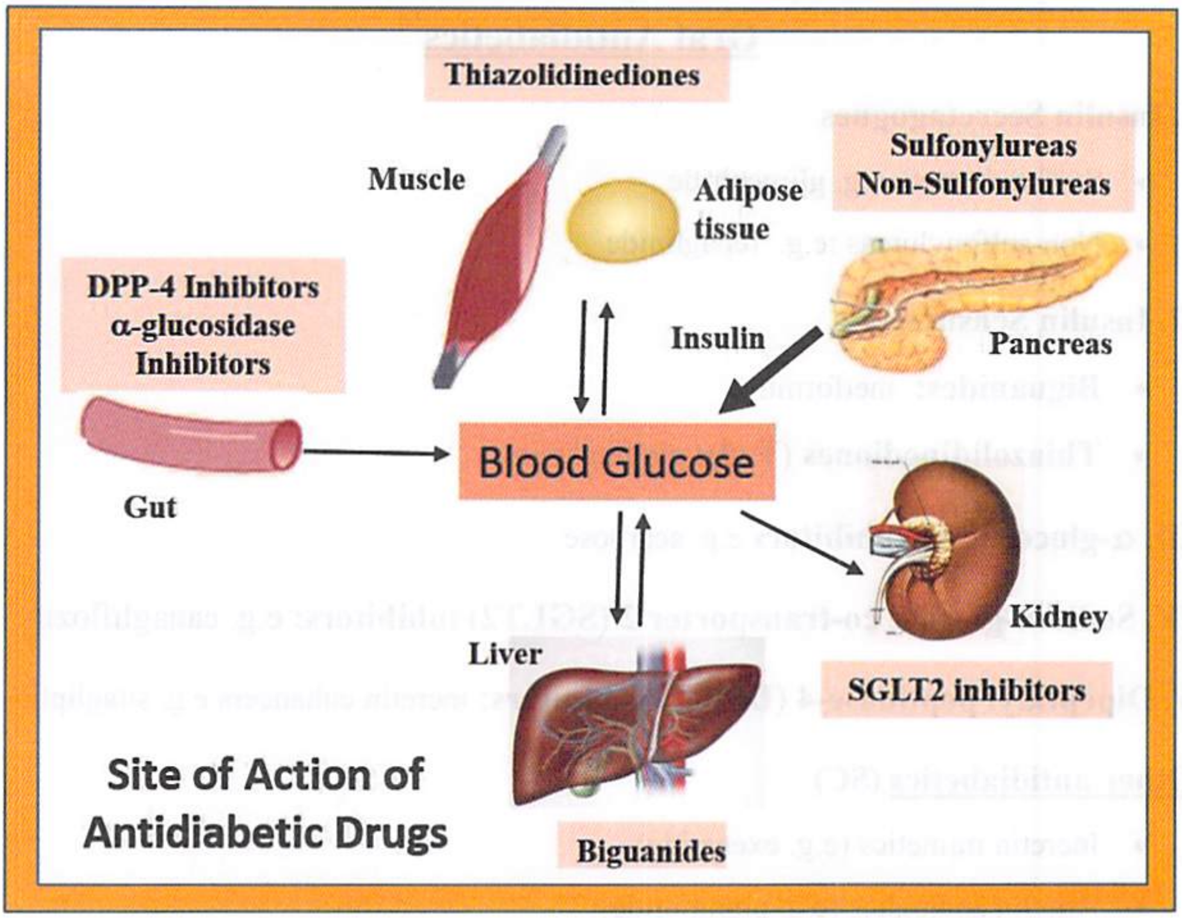
V. Dipeptidyl peptidase-4 (DPP-4) Inhibitors: incretin enhancers e.g. sitagliptin

Other antidiabetics (SC)

- Incretin mimetics (e.g. exenatide)
- Amylin analogues (e.g. pramlintide)

---

[14] Expected ↓ in A_{1C} with monotherapy: sulfonylureas or biguanides (1-2%), non sulfonylureas or Tzd (0.5-1.5%), α-glucosidase inhibitors or DPP-4 inhibitors(0.5–0.8%), insulin (1.5-3.5%).


Thiazolidinediones
Muscle
Adipose tissue
Sulfonylureas
Non-Sulfonylureas
DPP-4 Inhibitors
α-glucosidase Inhibitors
Insulin
Pancreas
Gut
Blood Glucose
Kidney
Liver
SGLT2 inhibitors
Biguanides

Site of Action of Antidiabetic Drugs

I. Insulin Secretagogues

A. Sulfonylureas

Mechanism of Action

- ↑ Insulin secretion by binding with specific receptors on β cell membrane linked to ATP-sensitive K^+ channels (K^+_{ATP}) → blocks channels → depolarization → Ca^{2+} influx → insulin release from granules (**Main action**).
- ↓ Glucagon on chronic use.

Indication:

- **Type 2 DM**: If initial therapy with metformin + diet control + exercise fail or if metformin is contraindicated.

Sulfonylurea Preparations

1st Generation: tolbutamide[15]

- Less frequently used due to adverse effects & drug interactions.

2nd Generation

- 150 times more potent than 1st generation. (↑ receptor affinity).
- Fewer adverse effects & interactions.

Members:

- **Glipizide** (short acting)[16].
- **Gliclazide**[17] (intermediate acting)
- **Glibenclamide** (long acting - more hypoglycemic risk).
- **Glimepride**[18]: long acting (24 h) given once/day.

  Acts on a different receptor at K^+ ATP channel.

---

[15] Other 1st generation agents: chlorpropamide, tolazamide, acetohexamide.

[16] Glipizide: (6 - 12 h), gliclazide: (15 h), glibenclamide (24 h).

[17] Available as modified release tablets (MR) for once daily use.

[18] Peak effect is after 2-3 h so should be given before the main meal.

Contraindications of Sulfonylureas

1. Past history of allergy to sulfa compounds.
2. Type 1 DM as they require functioning β cells.
3. DM with pregnancy & lactation: they cross placenta & are excreted in milk → hypoglycemia in fetus & newborn.
4. DM with stress, e.g. infection, surgery, trauma or myocardial infarction (ineffective and ketoacidosis is liable to occur as stress increases insulin requirements).
5. DM with liver or renal disease→ ↑ risk of hypoglycemia as their action is prolonged since they are metabolized in liver & are excreted in urine.

Adverse Reactions

1. **Hypoglycemia:** more with drugs with long $t_{1/2}$ as glibenclamide particularly if elimination is impaired e.g. in elderly, renal or liver disease.
2. Hypersensitivity: drug allergy as skin rash.
3. Heavy weight (weight gain).

B. Nonsulfonylureas Secretagogues[19]

(Meglitinides, e.g. Repaglinide)

Mechanism of Action:

- Similar to that of sulfonylureas.

Advantages

- Very rapid onset with shorter duration than sulfonylureas→ brief stimulation of insulin secretions →
  a. **Less hyperglycemia** postprandially (↑ insulin secretion immediately after meal).
  b. **Less hypoglycemia** during late postprandial phase (less insulin secreted several hrs after meal).
- May be used in patients with a past history of allergy to sulfa compounds.

Disadvantages & adverse effects

- Frequent dosing (3 times/day; prandial)
- Weight gain (less than sulfonylureas).
- Mild hypoglycemia (less than sulfonylureas).

Precautions:

- Repaglinide should be used cautiously in liver impairment.

---

[19] Others: nateglinide

II. Insulin Sensitizers

A. Biguanides

(Metformin)

Mechanism of Action (not fully understood)[20]

1. ↓Hepatic glucose production by inhibiting gluconeogenesis (Main effect).
2. Direct stimulation of glycolysis in skeletal muscles & adipose tissue → rapid removal of glucose from blood with slight ↑ in blood lactate.
3. ↓ Intestinal glucose absorption with mild anorectic action.

Advantages of metformin

- No increase in body weight→ ↓ Insulin resistance.
- No hypoglycemia (i.e. euglycemic acts in hyperglycemia only).
- No drug interactions (no plasma proteins binding or hepatic metabolism).

Indications of Metformin[21]

- Initial therapy of type 2 diabetes together with diet regulation & exercise.

Side Effects

1. **GIT**: Metallic taste, anorexia, dyspepsia & diarrhea (common, minimized by starting with small dose and gradually increasing it).
2. **Lactic acidosis** (dangerous but infrequent): Metformin is **CI** in renal failure, liver failure & severe hypoxia (as HF, MI, pneumonia and alcoholics) due to ↑ risk of lactic acidosis (anaerobic metabolism) in these patients.

---

[20] The molecular mechanism of action is via activation the adenosine monophosphate (AMP)-activated protein kinase (AMPK). AMPK-independent effects of the drug have recently been identified.

[21] - The use of metformin + insulin in type 1 DM is considered if an adult with type 1 diabetes and a BMI of 25 kg/m^2 or above wants to improve their blood glucose control while minimising their effective insulin dose.
- Metformin may be used in metabolic syndrome and polycystic ovary syndrome (off label use) to manage the associated insulin resistance.

B. Thiazolidinediones (TZDs)

(Pioglitazone)

- Euglycemics, with delayed therapeutic effect (since their mechanism of action involves gene regulation).

Mechanism of Action

Insulin sensitizers: agonists for PPAR-γ receptor[22], in muscle, fat & liver →:

i. Enhanced adipocytes differentiation with synthesis of new fat cells sensitive to insulin which → ↓ circulating fatty acids through:

  a. ↑ Uptake of circulating fatty acids into fat cells.

  b. ⊖ intracellular lipolysis → ↓ FFA mobilization to blood.

ii. ↓ Circulating FFA → ↓ insulin resistance → ↑ glucose uptake by skeletal muscles & fat cells & ↓ hepatic glucose production → ↓ blood glucose.

Indications

- Used as monotherapy[23] or in combination in type 2 DM.

Adverse Reactions [24]

- Weight gain.
- Fluid retention → edema→ **may precipitate heart failure in some patients**.

Precautions

- Avoid in heart failure & liver dysfunction.
- Monitor for signs/symptoms of liver injury during use.
- Consider risk of fracture prior to initiation and during therapy.

---

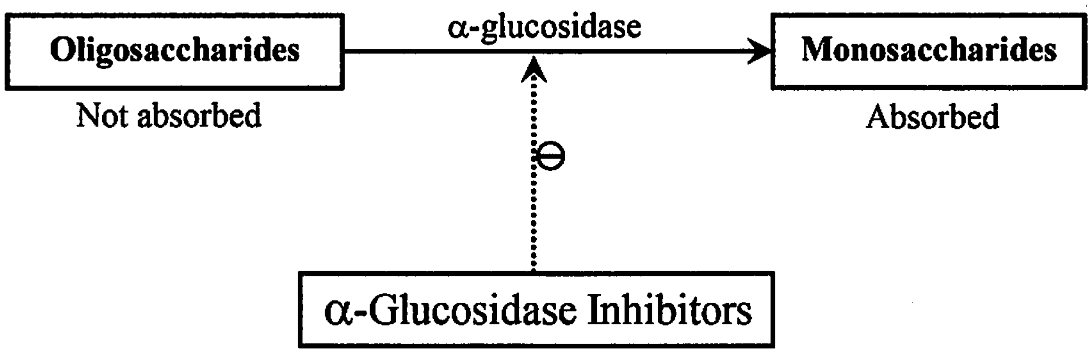
[22] The nuclear receptor peroxisome-proliferator activated receptor-gamma regulates insulin-responsive genes involved in carbohydrate & lipid metabolism & in adipocytes differentiation.

[23] If metformin & sulfonylurea are contraindicated.

[24] Rosiglitazone, another TZD,↑ LDL cholesterol, risk of stroke, heart failure & MI →suspended in Egypt.

III. Alpha Glucosidase Inhibitors

Acarbose - Miglitol


Oligosaccharides
α-glucosidase
Monosaccharides
Not absorbed
Absorbed
⊖
α-Glucosidase Inhibitors

Mechanism of Action

- Normal brush border of intestine contains α-glucosidase which converts oligosaccharides into monosaccharides (glucose) which are absorbed.
- Acarbose inhibits alpha glucosidase enzyme → ↓ glucose absorption.

Advantages

- Limits the postprandial rise in blood sugar → "**insulin sparing effect**".
- No hypoglycemia.

Indications

- Adjuvants to sulfonylureas in type 2 DM in patients intolerant to metformin.

Adverse Effects

- GIT upset: flatulence - abdominal pain - diarrhea.

N.B.: Symptoms are due to fermentation of undigested carbohydrates in colon → gas release.

IV. Sodium-glucose co-transporter 2 inhibitors

SGLT2 inhibitors

Canagliflozin – Dapagliflozin - Empagliflozin

Mechanism of Action

- Inhibit the sodium glucose transporter 2 in the proximal tubules of the kidney → prevents the reabsorption of filtered glucose in the kidney → removing excess glucose in the urine.
- Reduce HbA1c, weight, and blood pressure.

Indications[25]**:**

- Type 2 diabetes: monotherapy or combined with metformin or TZDs.

Advantage: Given orally once daily

Adverse effects:

- Infections in the genitourinary systems
- Mild hypoglycemia if used with insulin or other oral antidiabetic therapy
- Increased risk of bone fractures.

Precautions:

Adequate renal function needed.

---

[25] Its use in type 1 DM is under investigation

V. Dipeptidyl peptidase (DPP)-4 Inhibitors

Sitagliptin - Saxagliptin – Linagliptin -Alogliptin

Mechanism of Action

DPP-4 rapidly degrades incretins (e.g. GLP-1) that are released from GIT following meals to lower blood sugar. Inhibition of DPP-4 →↑ plasma incretins → ↑ glucose-dependent insulin secretion &↓glucagon secretion→↓postprandial hyperglycemia.

Indications: orally once daily

- Type 2 diabetes: monotherapy or combined with metformin or TZDs.

Adverse effects (well tolerated)

- Nasopharyngitis & upper respiratory infections - joint pain.

Subcutaneous Antidiabetics

1. GLP-1 receptor agonists (incretin mimetics; more stable than natural GLP-1)

Exenatide twice/day – Liraglutide once/day - Dulaglutide once /week

Mechanism of Action:

1. ↑glucose-dependent insulin secretion-↑acute responsiveness of β-cell to secrete insulin
2. Suppress inappropriately elevated postprandial glucagon secretion.
3. Slow gastric emptying, & reduce food intake (liraglutide is used in obesity).

Adverse effects: Nausea (most common, especially with high doses).

11. Amylin Analogues: Pramlintide

Mechanism of Action

Analogue of amylin (hormone co-secreted with insulin following food intake):

1. Decreases post prandial glucagon secretion.
2. Delays gastric emptying and improves satiety.

Indications:

- Type 1 & II diabetes, prior to meal, adjunct to insulin (but not in same syringe).

Adverse effects:

1. Hypoglycemia (reduce insulin dose by 50% on initiation of pramlintide therapy).
2. Nausea & vomiting- anorexia.

Management of Diabetes

The Four Cornerstones of Treatment of Diabetes are:

- Life style (diet regulation & exercise→ ↑ insulin receptors) – education – medication.

N.B.: Caloric restriction is not initially required in patients with type 1 DM (underweight), but is necessary when insulin therapy results in ↑weight.

Drug Therapy

A. Drug Therapy of Type 1 DM:

Insulin therapy[27]

- **Intensive therapy**[28]: multiple doses or insulin pump.
- **Conventional therapy**: 2 injections (mixture of intermediate & regular insulin; 2/3 of dose in the morning & 1/3 in the evening).
- Insulin dose should be increased during stress (infection, surgery, ...).

B. Drug Therapy of Type 2 DM: (If the HbA1C target is not achieved after 3 months, consider the next step)

- **Step 1 (monotherapy)**: lifestyle modification + metformin (unless contraindicated)
- **Step 2 (dual therapy)**[29]: lifestyle + metformin + basal insulin or another oral drug.
- **Step 3 (triple therapy)**: lifestyle + metformin + 2 other drugs (basal insulin may be one of them).
- **Step 4 :** lifestyle + metformin + basal insulin + mealtime insulin or GLP-1 agonist

N.B.:

- If initial therapy with metformin is CI or not tolerated → start with another oral drug.
- Consider initiating therapy with a dual or triple combination if A1C is ≥ 9%.
- Consider initiating combination insulin therapy if A1C is ≥ 10 especially if symptoms are present or any catabolic features are in evidence.

---

[27] The amylin analogue pramlintide may be added to insulin in management of type 1 DM.

[28] Intensive insulin for tight control is prescribed to all type 1 DM. & for type-2 patients requiring tight control. Long or intermediate insulins are used to cover basal insulin requirements. Short or ultrashort insulins are taken before each meal according to carbohydrate in meal & pre-meal blood glucose.

[29] The bile acid sequestrant colesevelam & the D2-dopamine agonist bromocriptine are considered among drug choices for dual & triple therapy by American Association of Clinical Endocrinologists.

Comas in Diabetes

A. Hypoglycemic Coma (see adverse effects of insulin & sulfonylureas)

B. Diabetic Ketoacidosis (Polyurea, vomiting, dehydration, ↑ respiration, coma)

Absolute insulin deficiency is due to stopping insulin or exposure to stress (surgery, infection...).

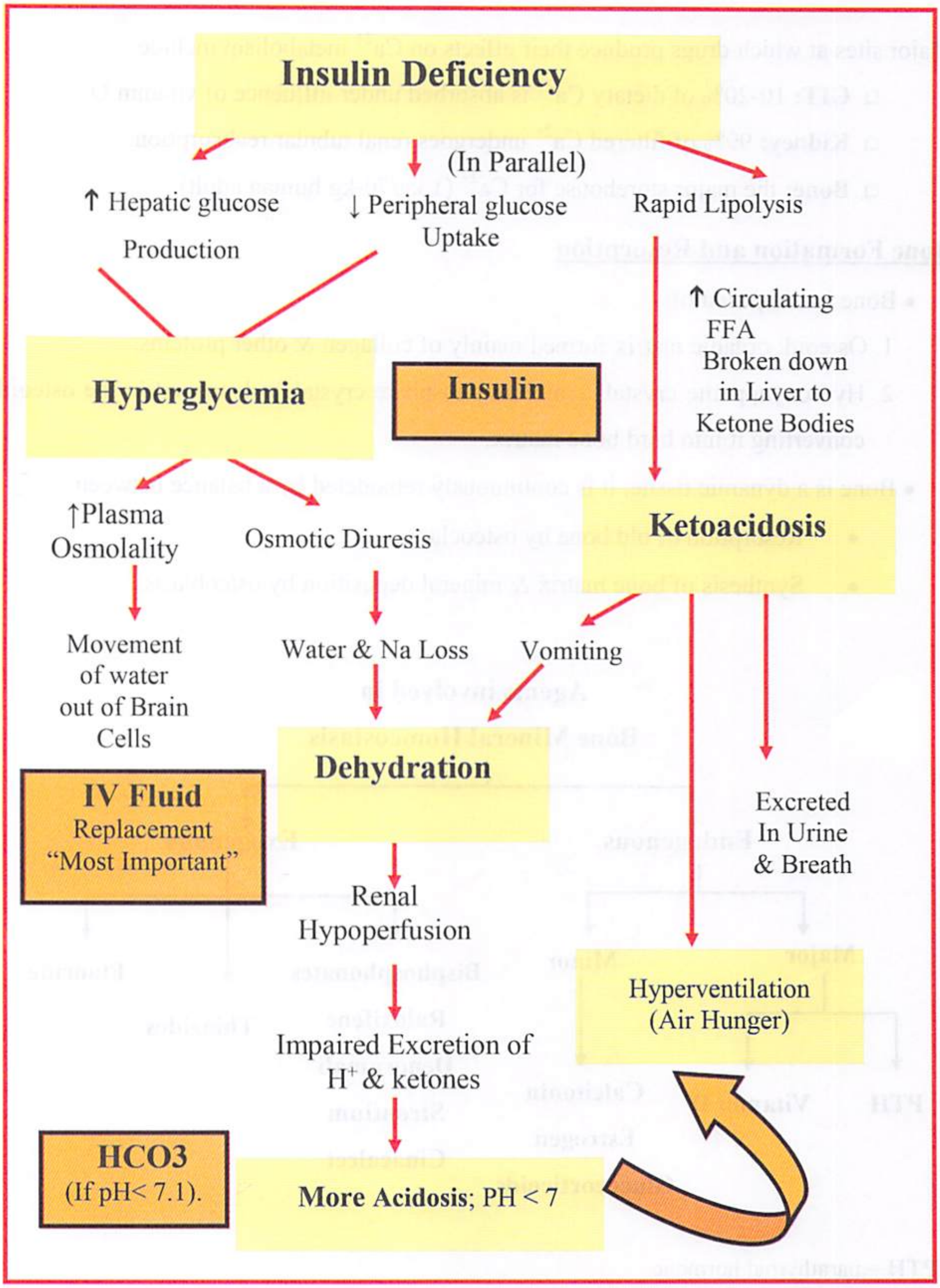
Management[30] (see fig)

1. **Fluid replacement** (3-5 L): 1st and most important.
    - Isotonic saline initially followed by half tonic solution if serum Na^+ rises.
    - 5% glucose if blood glucose falls to 250 mg/dl to maintain plasma osmolality thus avoiding brain edema & to avoid hypoglycemia.
2. **Insulin therapy**
    - Regular insulin (low dose IV infusion; or IM) until blood acetone disappears.
    - IV Dose: ↓ by half if blood glucose falls to 250 mg/dl.
    - Once patient is stable & eats & drinks normally, switch to 4 times/d SC.
3. **Potassium Replacement**
    - Initial K^+ level is often high due to acidosis & there is no need for K+.
    - Insulin reverses acidosis → intracellular shift of K^+ → ↓ serum K^+ level requiring KCl administration according to K^+ level:
        - 20 mmol/l (if normokalemic)
        - 40 mmol/l (if hypokalemic).
4. **Bicarbonate**
    - Mild acidosis is spontaneously corrected by insulin.
    - Bicarbonate is given in severe acidosis (pH < 7.1) and should be stopped when pH reaches 7.2.
5. **Treat underlying cause:** e.g. infection (as perianal abscess) with broad spectrum antimicrobials.

---

[30] This treatment plan is an example of different treatment plans for diabetic ketoacidosis. Different hospitals follow different plans.

Management of Metabolic Disturbances in Diabetic Ketoacidosis


Insulin Deficiency
(In Parallel)
↑ Hepatic glucose Production
↓ Peripheral glucose Uptake
Rapid Lipolysis
↑ Circulating FFA
Broken down in Liver to Ketone Bodies
Hyperglycemia
Insulin
Ketoacidosis
↑Plasma Osmolality
Osmotic Diuresis
Movement of water out of Brain Cells
Water & Na Loss
Vomiting
Dehydration
IV Fluid Replacement "Most Important"
Excreted In Urine & Breath
Renal Hypoperfusion
Impaired Excretion of H+ & ketones
Hyperventilation (Air Hunger)
HCO3 (If pH< 7.1).
More Acidosis; PH < 7

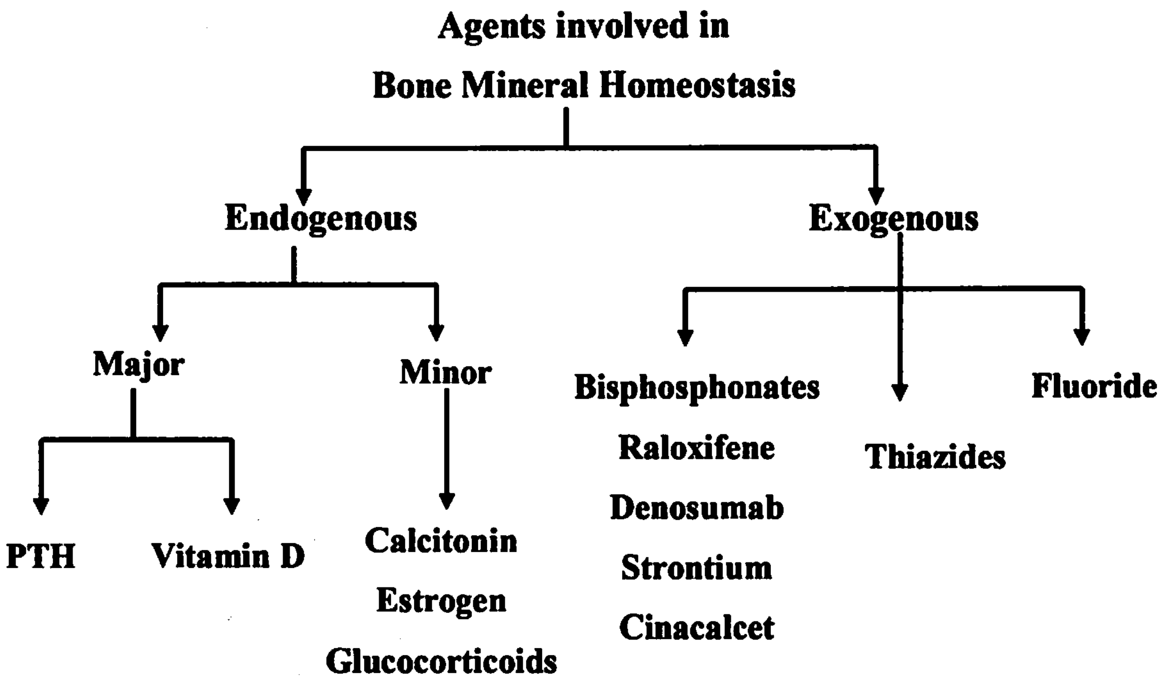
AGENTS AFFECTING BONE CALCIUM HOMEOSTASIS

Major sites at which drugs produce their effects on Ca^{2+} metabolism include:

- **GIT:** 10-20% of dietary Ca^{2+} is absorbed under influence of vitamin D.
- **Kidney:** 99% of filtered Ca^{2+} undergoes renal tubular reabsorption.
- **Bone:** the major storehouse for Ca^{2+} (1 kg/70-kg human adult).

Bone Formation and Resorption

- Bone is composed of:
  1. Osteoid: organic matrix formed mainly of collagen & other proteins.
  2. Hydroxyappatite crystals (calcium phosphate crystals): deposited in the osteoid converting it into hard bone matrix.
- Bone is a dynamic tissue; it is continuously remodeled by a balance between:
  - Resorption of old bone by osteoclasts.
  - Synthesis of bone matrix & mineral deposition by osteoblasts.


Agents involved in
Bone Mineral Homeostasis
Endogenous
Exogenous
Major
Minor
PTH
Vitamin D
Calcitonin
Estrogen
Glucocorticoids
Bisphosphonates
Raloxifene
Denosumab
Strontium
Cinacalcet
Thiazides
Fluoride

PTH = parathyroid hormone.

A. Endogenous Agents Affecting Bone Calcium Homeostasis

1. Vitamin D

Mechanism of Action

- The active metabolite of vitamin D (calcitriol) enters the nuclei of target cells → stimulate production of specific mRNA → directs ribosomal synthesis of Ca^{2+}-PO_4^{3-} carrier proteins necessary for Ca^{2+} transport.

Actions

Increases serum Ca^{2+} & PO_4^{3-} levels through:

1. **GIT:** stimulates Ca^{2+} & PO_4^{3-} absorption by small intestine.
2. **Bone:** ↑ bone resorption by osteoclasts (excess vitamin D in normal)
   Stimulates osteoblasts → Ca^{2+} deposition (in rickets).
3. **Kidney:** ↑ Ca^{2+} & PO_4^{3-} proximal tubular reabsorption.

Indications of vitamin D

1. Prevention and cure of rickets in children & osteomalacia in adults.
2. Osteoporosis.
3. Hypoparathyroidism.

Peparations

- Vitamin D_2 is derived from plants & Vitamin D_3 is produced in skin by ultraviolet rays, both are present in diet.
- Vitamin D is activated by hydroxylation first in liver (25 -OH) then renally (1-α-OH) under PTH control.

Important preparations include:

1. **Dihydrotachysterol (AT 10):** D_2 analog (requires activation)
2. **1-α-(OH) D_3 (alfacalcidiol)**
3. **1, 25-$(OH)_2$ D_3 (calcitriol)**

Alfacalcidiol & calcitriol are used in renal rickets & renal failure (do not require renal activation).

II. Parathyroid Hormone (PTH)

- Secreted by parathyroid gland.
- Secretion is increased by ↓ Ca^{2+} & ↑ PO_4^{3-} (reverse is true).

Actions: ↑ serum Ca^{2+} & ↓ PO_4^{3-} levels through:

1. **Bone:**
   - ↑ bone turnover (bone remodeling ; resorption followed by formation):
     - ↑ PTH (e.g., tumor) → bone resorption →↑ **serum Ca^{2+}**.
     - Low dose (intermittent) → bone formation.
2. **Kidney:**
   a. Enhances Ca^{2+} reabsorption.
   b. Blocks phosphate reabsorption → phosphaturia.
   c. Stimulates production of active form of vitamin D (calcitriol) which promotes intestinal absorption of Ca^{2+} and PO_4^{3-}.

Uses:

- Osteoporosis: **Teriparatide** (recombinant PTH); stimulates bone formation.

Adverse effects of Teriparatide : Dizziness & tachycardia

III. Calcitonin

- Secreted by parafollicular cells of thyroid gland in response to ↑ plasma Ca^{2+}.

Actions: ↓ serum Ca^{2+} & PO_4^{3-} levels through:

1. **Bone:**
   - ↓ Bone resorption - ↓ Rate of bone turnover.
2. **Kidney:**
   - ↓ Reabsorption of Ca^{2+} & PO_4^{3-} at proximal convoluted tubules → ↑ excretion.

Indications

1. Paget's disease[31].
2. Hypercalcemia.

Adverse effects:

1. Nausea, vomiting, bad taste.
2. Flushing of the face, swelling of hand.
3. Runny nose, nasal bleeding & nasal irritation (with nasal spray).

Preparations

- Porcine calcitonin
- Salmon calcitonin (↑ $t_{½}$ & ↑ potency) .
- Human calcitonin.

Actions of PTH, Vitamin D and Calcitonin

	PTH	Vitamin D	Calcitonin
GIT Absorption	↑ Ca^{2+} & PO_4^{3-}	↑ Ca^{2+} & PO_4^{3-}	↓ Ca^{2+} & PO_4^{3-}
BONE	↑ Resorption	↑ Resorption (in normal) or formation (in rickets)	↓ Resorption
RENAL Reabsorption	↑ Ca^{2+} ↓ PO_4^{3-}	↑ Ca^{2+} ↑ PO_4^{3-}	↓ Ca^{2+} ↓ PO_4^{3-}
Serum Ca^{2+} & PO_4^{3-}	↑ Ca^{2+} ↓ PO_4^{3-}	↑ Ca^{2+} ↑ PO_4^{3-}	↓ Ca^{2+} ↓ PO_4^{3-}

---

[31] Uncontrolled osteoclastic bone resorption & 2ry ↑ bone formation (expanded & poorly mineralized).

IV. Estrogens

- Inhibit bone resorption induced by parathyroid hormone.

Indications: Prevention & treatment of osteoporosis in post menopausal women (hormone replacement therapy may increase risk of cancer).

V. Glucocorticoids

Actions: ↓ Serum calcium level and bone collagen through:

1. Anti-vitamin D → ↓ activation of vitamin D in liver, thus ↓ Ca^{2+} absorption from intestine.
2. Catabolic → ↓ bone collagen synthesis.

Indications:

- Hypercalcemia due to: malignancy - Vitamin D intoxication.

Chronic systemic use of glucocorticoids causes osteoporosis.

B. Exogenous Agents Affecting Bone Calcium Homeostasis[32]

1. **Bisphosphonates** (Etidronate, pamidronate & alendronate)
    1. Bind directly to bone → retard dissolution & formation of hydroxyappatite crystals (inhibit bone turnover, mechanisms is unclear).
    2. Inhibits an enzyme necessary for osteoclasts survival (alendronate).
    3. Inhibition of 1, $25(OH)_2$ D production & intestinal Ca^{2+} transport.

Indications

1. Hypercalcemia associated with malignancy.
2. Osteoporosis[33] by increasing bone mineral density.
3. Paget's disease of bone: ↓ bone turnover.

Adverse effects, CI & precautions

- Gastric & esophageal irritation (take with a full glass of water while sitting upright for 30 min) → CI: peptic ulcer - esophageal motility disorders.
- Osteonecrosis of the jaw
- Given cautiously in renal impairment.

2. **Raloxifene**:

- Selective estrogen receptor modulator (partial agonist) with effects similar to estrogen on bone (inhibits bone resorption) but not on breast or uterus → no risk of cancer.

Adverse effects & Contraindications

- Hot flashes, sweating, or leg cramps.
- Thrombophlebitis & thromboembolism (CI history of venous thrombo-embolism).

---

[32] Mithramycin: (cytotoxic antibiotic→ thrombocytopenia) & gallium nitrate (nephrotoxic): ↓ bone resorption. Used in hypercalcaemia & Paget's disease (resistant cases).

[33] Daily,weekly, monthly, every 3 months schedules of several bisphonates as well as annual infusions of zoledronate, are available. Beneficial effects persist over several years, but discontinuation results in a gradual loss of effects.

3. Denosumab

- Monoclonal antibody that inhibits RANKL[34] → inhibits osteoclast formation & function → **inhibits bone resorption**.
- Uses: postmenopausal osteoporosis in women at high risk of fracture & those intolerant or unresponsive to other osteoporosis therapies.
- Subcutaneous injection every 6 months.

Adverse effects:

1. Increased risk of infections
2. Dermatological reactions.
3. Hypocalcemia, osteonecrosis of the jaw and atypical fractures.

4. Strontium

- ↑ Bone formation (calcimimetic, stimulates Ca^{++} sensing receptors causing pre-osteoblasts to differentiate into osteoblasts).
- Inhibits bone resorption (inhibits osteoclasts).
- Uses: severe osteoporosis, prevents fractures in older women.
- Side effects: May induce myocardial infarction & allergic reactions.

5. Cinacalcet

- Calcimimetic: ↑Sensitivity of parathyroid Ca^{++} sensing receptors[35] to blood Ca^{++} conc. → ↓ PTH secretion→ ↓ Ca^{++}→ used in hyperparathyroidism.

6. Fluoride

- Accumulates in bone → stabilizes hydroxyappetite crystals (unknown mechanism.)
- ↑ Bone formation - ↑ mineral content of bone.
- Given with Ca^{2+} supplements (may cause osteomalacia if given alone).
- Uses: Prophylaxis in dental caries (in tooth paste) - osteoporosis (investigational).

7. Thiazides: decrease renal Ca^{2+} excretion→ ↓ Kidney stone formation.

---

[34] RANKL: receptor activator of nuclear factor kappa-B ligand.

[35] Antagonists to Ca^{++} sensing receptors are being developed & may be used in hypothyroidism & to stimulate intermittent PTH secretion in treatment of osteoporosis.

Disturbances in Calcium Homeostasis & their Management

I. Hypercalcemia (→ polyuria → dehydration & coma) due to:

- 1^{ry} Hyperparathyroidism - cancers[36] - hypervitaminosis D.
- Thiazides – immobilization - sarcoidosis.

Treatment

1. **Saline diuresis**
   - Initial infusion of saline → reverses dehydration & restores urine flow resulting in diuresis &↑ Ca^{2+} excretion (frusemide may be added to ↑ urine flow & inhibit Ca^{2+} reabsorption → ↓ serum Ca^{2+}).
2. **Other measures (more prolonged medical treatment)**[37]

   Bisphosphonates - calcitonin - glucocorticoids.

II. Hypocalcemia (tetany, paresthesia, muscle cramps, convulsions) due to:

- Hypoparathyroidism - Ca^{2+} or vitamin D deficiency - renal failure.

Treatment

- **Acute:** calcium gluconate 10% slowly IV.
- **Chronic:**
  1. Calcium gluconate tablets.
  2. Vitamin D and AT 10.
  3. $Al(OH)_3$: binds phosphate in gut → hypophosphatemia → ⊕ formation of active Vit. D → ↑ Ca^{2+} absorption.

III. Rickets & Osteomalacia [poor bone mineralization (↓ Ca^{2+} or PO_4^{3-})]

A. Treatment of Nutritional Osteomalacia and Rickets

Calcium + vitamin D (IM in malabsorption).

B. Treatment of Renal rickets (failure of renal activation of vitamin D)

Calcium + calcitriol or alfacalcidiol (do not require renal activation).

---

[36] Tumors secreting PTH–like substance.

[37] Mithramycin and gallium nitrate may also be given. Phosphate IV; if others fail but dangerous→sudden hypocalcemia & acute renal failure.

IV. Osteoporosis (↓ bone mass → ↑ risk of fractures, with normal mineralization of remaining bone)

Causes

1. Estrogen or androgen deficiency (most common in postmenopausal females and may occur in older men).
2. Cushing's disease (↑ glucocorticoids) - Thyrotoxicosis.
3. **Chronic use of**: heparin - aluminum antacids- phenytoin- proton pump inhibitors.
4. Immobilization.

Treatment of osteoporosis

I. Drugs ↓ Bone Resorption

- Bisphosphonates (Alendronate).
- Raloxifene.
- Denosumab.
- Cyclic Estrogen (post menopausal ; mainly).

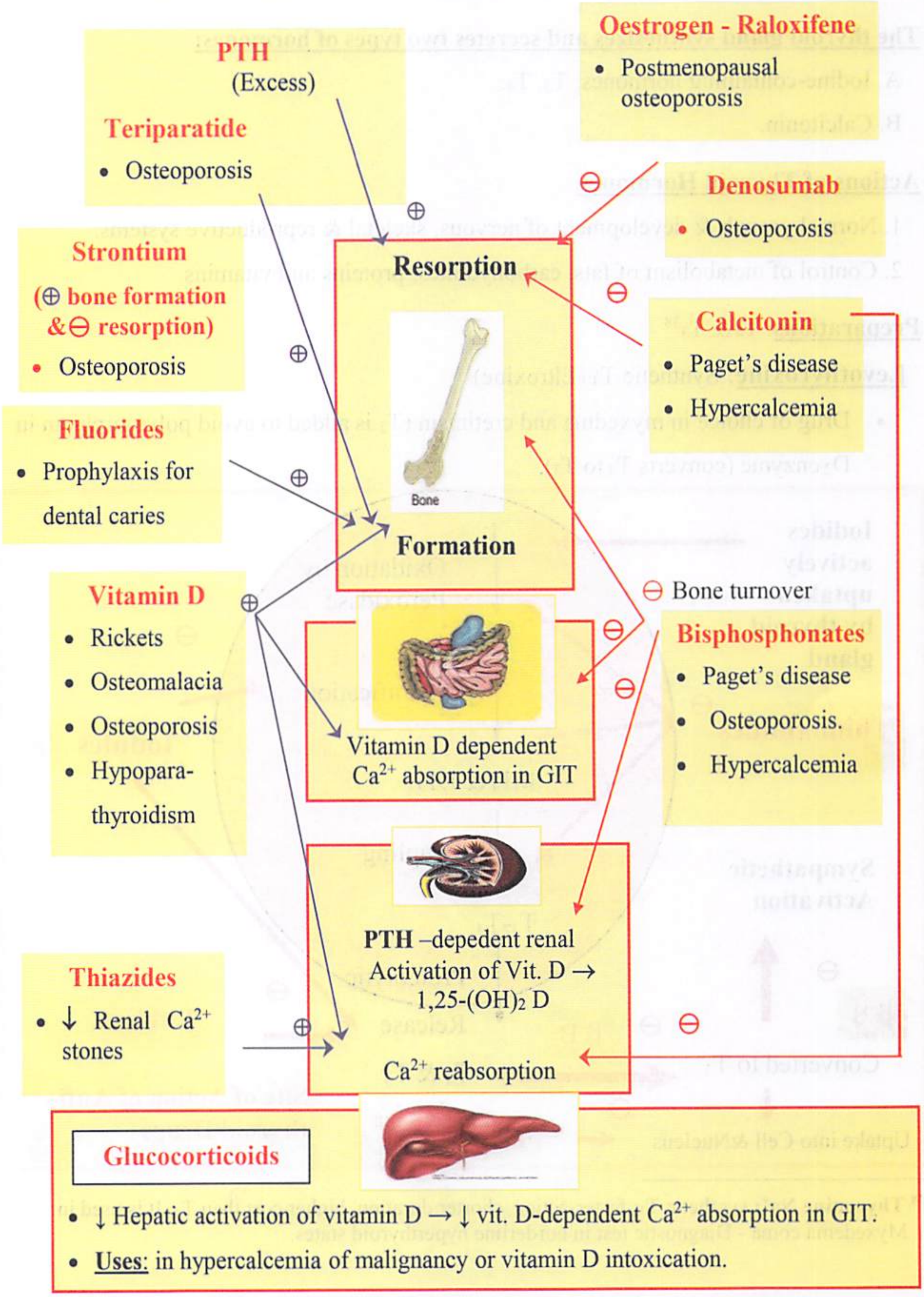
II. Drugs ↑ Bone Formation

- Teriparatide.
- Anabolic steroids (post-menopausal & in elderly males).

III. Others

- **Ca^{2+} & vitamin D** (idiopathic osteoporosis in men & post-menopausal women).
- **Strontium** (reserved for severe osteoporosis).

Actions & Uses of Agents Affecting Bone Ca Metabolism



PTH
(Excess)

Teriparatide
- Osteoporosis

Oestrogen - Raloxifene
- Postmenopausal osteoporosis

Denosumab
- Osteoporosis

Strontium
(⊕ bone formation &⊖ resorption)
- Osteoporosis

Calcitonin
- Paget's disease
- Hypercalcemia

Fluorides
- Prophylaxis for dental caries

Resorption

Formation

⊖ Bone turnover

Bisphosphonates
- Paget's disease
- Osteoporosis.
- Hypercalcemia

Vitamin D
- Rickets
- Osteomalacia
- Osteoporosis
- Hypoparathyroidism

Vitamin D dependent Ca^{2+} absorption in GIT

PTH –depedent renal Activation of Vit. D → 1,25-$(OH)_2$ D

Ca^{2+} reabsorption

Thiazides
- ↓ Renal Ca^{2+} stones

Glucocorticoids
- ↓ Hepatic activation of vitamin D → ↓ vit. D-dependent Ca^{2+} absorption in GIT.
- **Uses:** in hypercalcemia of malignancy or vitamin D intoxication.

THYROID HORMONES AND ANTITHYROID DRUGS

The thyroid gland synthesizes and secretes two types of hormones:

A. Iodine-containing hormones: T_3, T_4.

B. Calcitonin.

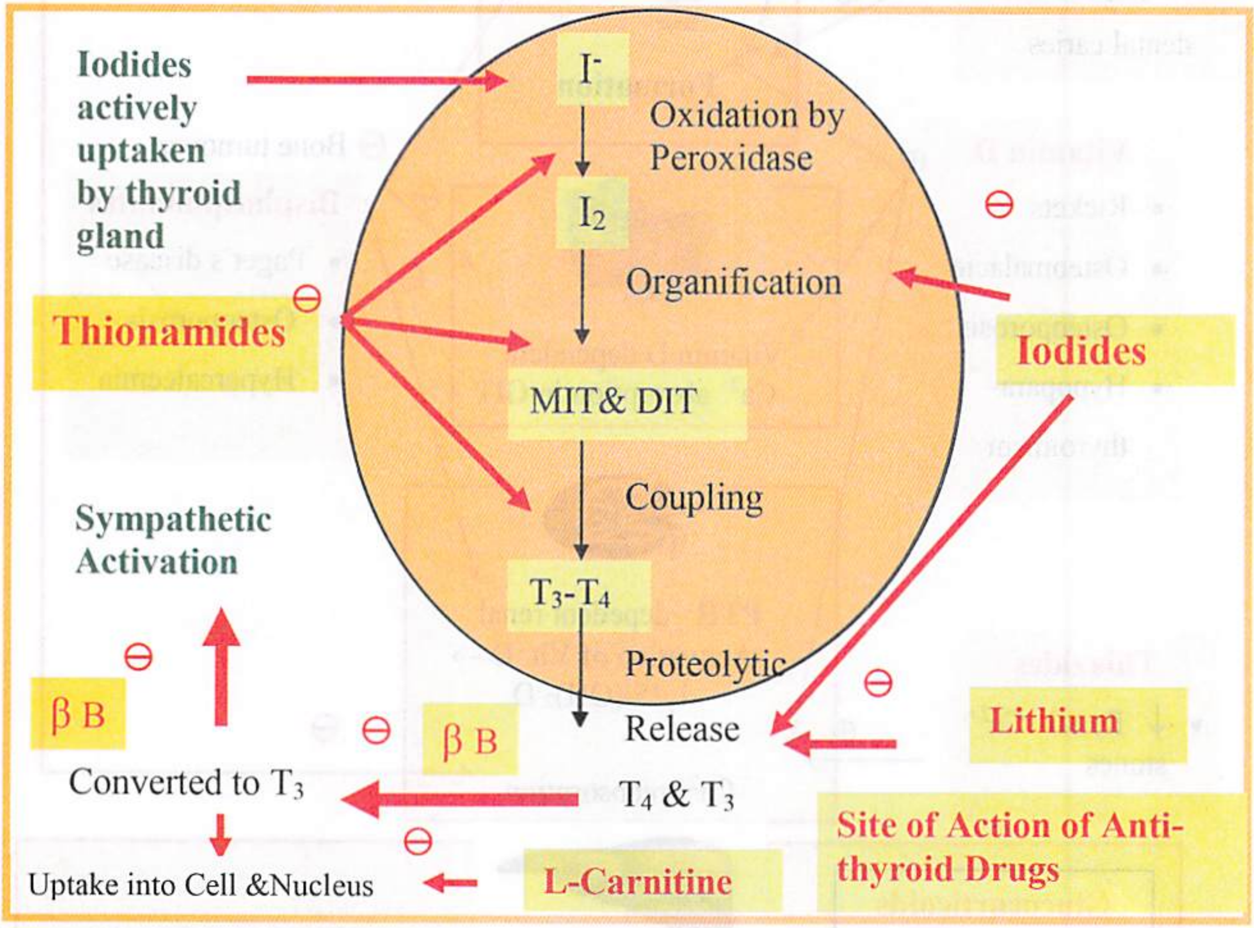
Actions of Thyroid Hormones

1. Normal growth & development of nervous, skeletal & reproductive systems.
2. Control of metabolism of fats, carbohydrates, proteins and vitamins.

Preparations: T_4 & T_3[38]

Levothyroxine: Synthetic T_4 (Eltroxine)

- Drug of choice in myxedma and cretinism (T_3 is added to avoid polymorphism in D_2 enzyme (converts T_4 to T_3).


Iodides actively uptaken by thyroid gland
I^-
Oxidation by Peroxidase
I_2
Organification
Thionamides
⊖
⊖
Iodides
MIT& DIT
Coupling
Sympathetic Activation
T_3-T_4
Proteolytic Release
⊖
βB
⊖
βB
⊖
Lithium
Converted to T_3
T_4 & T_3
Site of Action of Anti-thyroid Drugs
⊖
Uptake into Cell &Nucleus
L-Carnitine

---

[38] **Thyronine Na$^+$:** synthetic T_3; faster-acting, shorter duration, higher cost than T_4. It is used in: Myxedema coma - Diagnostic test in borderline hyperthyroid states.

Synthesis & Secretion of T_3 and T_4[39] & Antithyroid Drugs

Synthesis & Secretion of T_3 & T_4	Antithyroid Drugs
I. Iodide trapping • Iodides are actively uptaken from blood by thyroid gland. • Uptake is stimulated by TSH	• Oral I^{131} is trapped & concentrated in thyroid gland to emit β rays.
II. Oxidation • Iodide is oxidizesd to iodine by thyro-peroxidase enzyme.	• Inhibited by thionamides
III. Organification • Iodination of tyrosine residues on thyroglobulin → formation of monoiodotyrosine (MIT) & diiodotyrosine (DIT).	• Inhibited by thionamides & high doses of iodides
IV. Coupling • MIT and DIT are coupled to form T_4 and T_3 stored in the follicles as thyroglobulin.	• Inhibited by thionamides.
V. Release • Proteolytic release of T_4 &T_3 from thyroglobulin (bound to thyroxine binding globulin in blood	• Inhibited by iodides and lithium carbonate
VI. Conversion • T_4 is converted to T_3 by $5'$ deiodinase in peripheral tissues.	• Inhibited by propranolol propylthiouracil & corticosteroids
VII. Tissue uptake: entry into cell nucleus to induce effects (activity of T_3: 3-4 times> T_4).	• L-Carnitine

---

[39] Iodine, necessary for synthesis of thyroid hormones, is derived from ingested food or iodine supplements given orally. Ingested iodine is converted into iodide.

ANTI-THYROID DRUGS
(ATD)[40]
I. Thionamides

Members:

- Propylthiouracil (PTU)
- Methimazole (preferred as it is given once daily) (MMI)

Mechanism of Action

1. Prevent thyroid hormone synthesis by inhibiting peroxidase enzyme → inhibition of iodide oxidation, organification & coupling of MIT & DIT.
2. PTU: inhibits peripheral conversion of T_4 to T_3 → conversion of T_4 to rT_3 (inactive).

Therapeutic Uses

1. Hyperthyroidism: treatment is continued for 1-2 years (most useful in young patients with small gland and mild disease)[41].
2. Preparation for subtotal thyroidectomy (very large gland or multiple nodular goiters): Treatment is continued until patient is euthyroid.
3. To reduce thyrotoxic symptoms while waiting for radioactive iodine to act.
4. Thyrotoxic crisis (PTU inhibits conversion of T_4 to T_3).

Adverse Effects[42]

1. Maculopapular rash (most common).
2. Immune reactions e.g. agranulocytosis (most serious; but rare)[43].
3. Hepatic necrosis (with PTU); cholestatic jaundice.
4. Fetal goitre with MMI (PTU is preferred during pregnancy) ; crosses placenta as MMI but is extensively bound to plasma proteins).

---

[40] **Ipodate**: iodinated radio-contrast media. Inhibits hormone release & conversion of T_4 to T_3. Used as an alternative to iodides or thionamides if they are contraindicated - adjuvant in thyroid storm.

[41] It is preferred to combine ATD and thyroid hormone to avoid frequent adjustments of ATD doses.

[42] Lithium has been used to block release of thyroid hormone in patients intolerant to ATDs.

[43] WBC counts prior to initiating ATD, since mild leukopenia is common in Graves' disease. A baseline WBC is useful for comparison if subsequent WBC counts are obtained.

II. Iodide Salts and Iodine

Pharmacological Actions (high doses)

1. Inhibits organification.
2. Inhibit thyroid hormone release by inhibiting proteolysis.
3. Decrease size and vascularity of hyperplastic thyroid gland.

Escape Phenomenon

- Iodides lose their effectiveness after 2 weeks. This is due to compensatory ↑ in TSH which stimulates T_3 & T_4 release with loss of iodide effect.

Indications [rapid onset of action (1-2 days)]

1. Thyrotoxic crisis or storm.
2. Preparation for thyroidectomy.

Preparations: Lugol's iodine (iodine in potassium iodide).

III. Radioactive Iodine

Mechanism of Action

1. Oral I^{131} is rapidly absorbed and concentrated by the thyroid gland.
2. It emits β rays (cytotoxic) with poor penetration causing severe damage of the thyroid without damaging surrounding structures.

Indications

1. Hyperthyroidism in adults over 45 years.
2. Hyperthyroidism in patients not fit for surgery.
3. Recurrence after medical or surgical treatment.

Adverse Reactions

1. Hypothyroidism.
2. Recurrence.
3. Radiation thyroiditis: ↑↑ release of thyroid hormones→ cardiac complications; avoided by pretreatment with ATDs prior to I^{131} to deplete hormone stored in gland.

Contraindicated: in young, pregnant & lactating (→genetic damage &cancer)

IV. β-Adrenoceptive Blockers

(Propranalol or Nadolol)[44]

1. Antagonize sympathetic overactivity in thyrotoxicosis (cardioprotective).
2. Inhibit conversion of T_4 to T_3 → divert T_4 to the inactive rT_3.

Indications

1. Symptomatic: controls thyrotoxic symptoms until antithyroid drugs or I^{131} work.
2. Storm: Thyroid storm.
3. Surgery: Preoperative medication for thyroidectomy.

Thyroid Crisis or Storm

- Occurs in untreated patients; precipitated by surgery, severe infection or illness.

Treatment (drugs are given parenterally or by nasogastric tube)

1. Propranolol: to antagonize sympathetic overactivity (cardioprotection).
2. PTU: to ↓ hormone synthesis & inhibit conversion of T_4 to T_3.
3. Iodides: 1-2 hours after propylthiouracil to ↓ hormone release[45].
4. Hydrocortisone: inhibits conversion of T_4 to T_3- adrenal support.
5. Lithium: to ↓ hormone release if patient is allergic to iodides or intolerant to PTU[46].
6. Correct fluid balance and hyperthermia - treat HF - arrhythmia.
7. Plasmapheresis and peritoneal dialysis in resistant cases.

Preparation of patients before thyroidectomy

- Antithyroid drugs until euthyroid (6 weeks).
- Beta blockers
- K iodide is given for 15 days prior to surgery (decrease size & vascularity of gland).
- Thyroid supplements after operation.

---

[44] Patients who cannot tolerate βBs may be treated with calcium channel blockers (diltiazem).

[45] Iodides will be utilized in synthesis of hormone if synthesis is not previously inhibited by PTU.

[46] L-carnitine supplementation may prevent symptoms in hyperthyroidism & thyroid storm.

CORTICOSTEROIDS

The adrenal cortex secretes a number of steroid hormones into circulation:

- Glucocorticoids: cortisol (hydrocortisone).
- Mineralocorticoids: aldosterone.
- Sex hormones.

I. Cortisol

- The major glucocorticoid in humans.
- Secretion is controlled by ACTH secreted from the anterior pituitary.
- Rate of secretion changes in a circadian rhythm governed by ACTH secretion that peaks in early morning & troughs at midnight.
- 95% of Cortisol (also all glucocorticoids and mineralocorticoids) circulates in blood bound to α globulin; Corticosteroid binding globulin (CBG).

II. Aldosterone

- Most important mineralocorticoid (inhibits Na^+ excretion & stimulates K^+ & H^+ excretion) with minimal glucocorticoid activity.
- Very important in regulating blood volume & pressure.

Control of Aldosterone Secretion

1. Renin-angiotensin system activation by hypovolemia & hyponatremia (most important).
2. Hyperkalemia.
3. ACTH (weak).

N.B.: 2^{ry} hyperaldosteronism occurs in CHF, liver cirrhosis, nephrosis.

Mechanism of Action of Corticosteroids

- They enter cells where they combine with steroid receptors in the cytoplasm forming a macro molecular complex which enters the nucleus where it interacts with chromosomal constituents and alters gene expression → effects on organs and tissues.

Pharmacological Actions, Adverse Effects & Precautions of Glucocorticoids

Pharmacological Actions	Adverse Effects & Precautions
I. Metabolic Effects • **Carbohydrates:** ↑ blood glucose: ⊕ Gluconeogenesis, ↓ glucose utilization.	- Hyperglycemia → diabetes. **CI: diabetes.**
• **Fat Metabolism:** Permissive effect on CA-induced lipolysis - redistributes fat from extremities to face, abdomen & shoulders.	- Moon face. - ↑ abdominal fat. - Buffalo hump - obesity.
• **Proteins Metabolism** Catabolic (except in liver).	- Muscle wasting: thin arms & legs. - Thinning of skin. - Retardation of growth (children). - Osteoporosis (↓ protein & Ca^{2+}).
• **Salt and Water Metabolism** ☐ ↓ Ca^{2+} absorption from GIT. ☐ Weak mineralocorticoid action: - ↑ Na^+ reabsorption. - ↑ K^+ excretion.	- Osteoporosis (CI). - Edema - ↑ weight. - Hypertension - heart failure (CI). - Hypokalemic alkalosis. **Precautions:** diet rich in K^+, Ca^{2+}, proteins and poor in Na^+.
II. Anti-inflammatory & immunosupressive • ↓ VD & edema of acute inflammation. • ↓ Healing - ↓ fibrosis. **Mechanism** • ↓ Eosinophils, macrophages, monocytes & lymphocytes conc., migration & function. • Inhibit cytokine release. • Inhibit phospholipase A_2 → ↓ PGs, LTs, PAF. • ↓ COX 2 expression.	- Mask manifestations of inflammation. -Delay healing of wounds. - Spread of infection. CI: severe infection, e.g. TB.
III. Adrenal suppression ☐ Prolonged use of high doses → ↓ ACTH ☐ Sudden withdrawal → acute adrenal insufficiency	Adrenal suppression: **To avoid**: - Use small doses (↑ in stress) & alternate-day schedules. - Carry card" I am on steroids". - Gradual withdrawal.
IV. GIT: ↑ HCl & pepsin - ↓ mucus.	Peptic ulcer (CI).
V. CNS: euphoria- behavioral changes.	Psychosis - depression (CI).
VI. Other effects: ↑Hemoglobin, RBCs, platelets & polymorphonuclear leukocytes	**Other side effects** - Glucoma, cataract. - Hirsutism, acne.

N.B.:

- Iatrogenic Cushing: adverse effects due to exogenous glucocorticoids.
- HPA axis suppression may occur if large doses are required for more than 2 weeks. Recovery of full adrenal function takes 2-18 months after withdrawal.

Preparations of Corticosteroids

A. Preparations with Primarily Glucocorticoid Activity

I. Cortisol (hydrocortisone)

Disadvantages of Cortisol

1. Mineralocorticoid activity.
2. Short duration: ($t_{½}$ dramatically ↑ in liver insufficiency).
3. Poorly absorbed through normal skin (but readily absorbed through inflamed skin & mucus membrane).

II. Synthetic Preparations

Prednisone - prednisolone - methylprednisolone – dexamethazone.

Advantages over Cortisol

1. Mineralocorticoid activity is less with **prednisolone** & absent with **dexamethazone.**
2. Longer duration of action.
3. More absorption through skin.

N.B.: Prednisone is preferred in pregnancy: minimal effect on fetus: Prodrug not activated in the fetus liver to the active form prednisolone. Any prednisolone formed by mother will be metabolized into prednisone by placental enzymes.

B. Preparations with Primarily Mineralocorticoid Activity

Fluodrocortisone

- Synthetic preparation with potent mineralocorticoid & glucocorticoid activity.

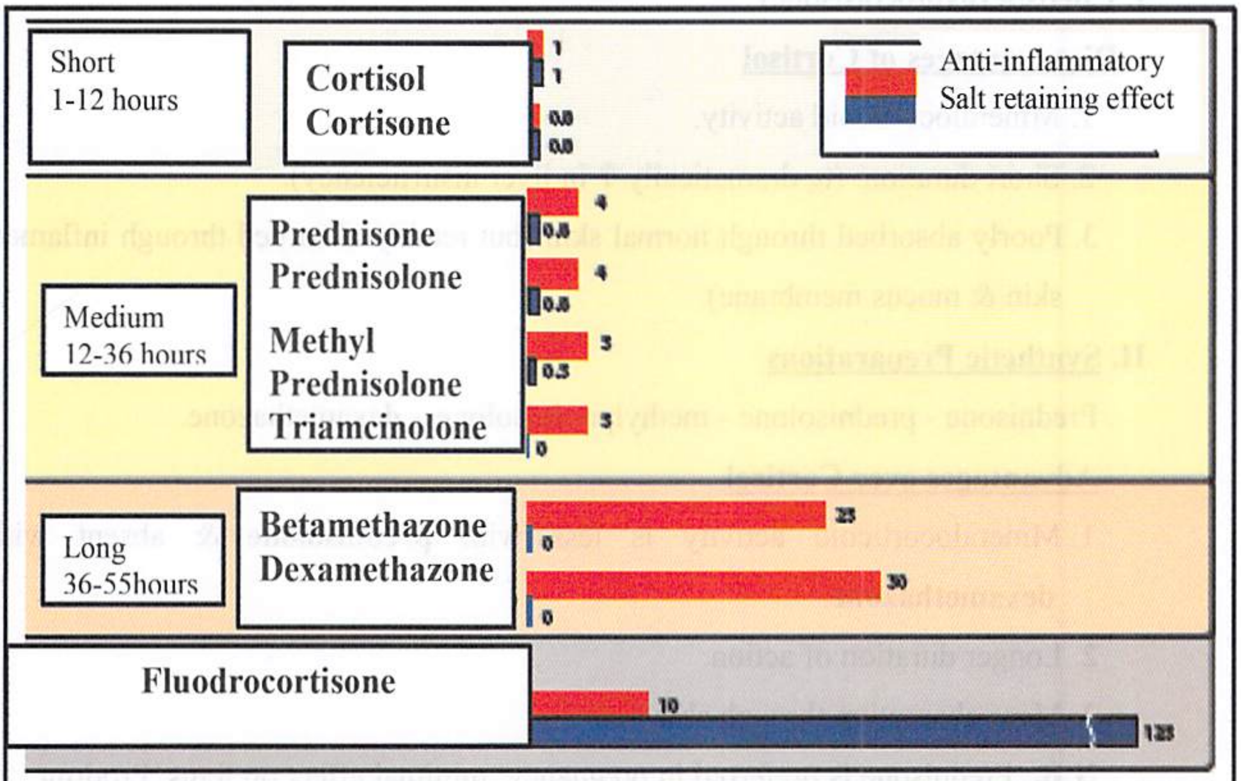
Fluodrocortisone is used for replacement therapy in hypoadrenal states, e.g. after adrenalectomy.

C. Preparations for Bronchial Asthma

- Beclomethazone, budesonide, fluticasone, triamcinolone, ciclesonide inhalation

Advantages in Asthma

1. Readily penetrate airway.
2. Very short half lives after entering the blood (if swallowed while being inhaled) due to extensive 1st pass metabolism so that systemic effects and toxicity are greatly reduced.



Corticosteroid Preparations
Activities are relative to that of cortisol (considered 1)

Adopted from Lippincot illustrated review (6 th Edition)

Therapeutic Uses

I. Adrenal Disorders

A. Acute Adrenal Insufficiency (Addisonian Crisis)

1. Saline & 5% glucose → maintain fluid & salt balance & blood sugar.
2. IV hydrocortisone hemisuccinate.
3. Fludrocortisone is started when total cortisol dose is ↓ to 50 mg/d.
4. Treat precipitating factors, e.g. antibiotics for infection.

B. Chronic Adrenal Insufficiency (Addison's disease)

1. Oral hydrocortisone: dose is ↑ during stress or surgery.
2. Fludrocortisone (orally): maintains Na^+ balance & BP.

II. Non-adrenal Disorders

A. Anti-allergic:

- Bronchial asthma
- Allergic conditions: skin, eye, GIT.

B. Immunosuppressants in:

- Autoimmune diseases: systemic lupus - rheumatoid arthritis.
- Organ transplantation, skin grafts.

III. Other Uses

1. Cerebral edema: ↓ VD - ↓ exudation of fluids.
2. Malignancies: ↓ lymphocytes in leukemia – lymphomas- ↑ appetite, hemoglobin, RBCs & platelets in patients on cytotoxic drugs.
3. Anti-stress in: bleeding - trauma - septic & anaphylactic shock (↑ VC effect of CA - ↑ glucose level, providing energy to counteract stress).
4. Hypercalcemia: anti-vit. D (↓ vit. D activation in liver → ↓ Ca^{2+} absorption).
5. Respiratory distress syndrome: accelerates lung maturation (IM 48 hrs before birth)

Inhibitors of the synthesis or function of adrenal steroids

- **Ketoconazole:** antifungal used in cushing disease (inhibits adrenal steroid synthesis).
- **Spironolactone**: aldosterone antagonist used in hyper-aldosteronism, heart failure, hypertension & in hirsutism in women (blocks androgen receptor in hair follicle).

SEX HORMONES

Female Hormones

- **Estrogen**
  - Estradiol
  - **(major ovarian estrogen)**
- **Progestins**
  - Progesterone

Male Hormones

- **Androgens**
  - Testosterone

Natural sex hormones are rapidly metabolized in the liver, therefore have low bioavailability so not used clinically.

Synthetic Estrogens

(Ethinylestradiol – Diethylstilbosterol)

Uses

1. Oral contraceptive pills.
2. Replacement therapy:
   a. Primary hypogonadism (in girls).
   b. Postmenopausal hormonal replacement therapy (HRT).
      - ↓ **Menopausal Symptoms:** flushing, sweating, mood changes.
      - ↓ **Osteoporosis.**
      - **Cardioprotective** ↓ LDL, ↑ HDL (prevents atherosclerosis).

Adverse Effects

1. Nausea - breast tenderness - weight gain.
2. Endometrial hyperplasia - ↑ risk of endometrial & breast cancer.
3. Hypertension & thromboembolim (↑ blood coagulation).
4. In male: feminization - impotence - ↓ libido - gynecomastia.

Synthetic Progestins

(Norethindrone – Norgestrel - medroxyprogesterone)

Uses

1. Hormonal contraception (major use).
2. Dysmenorrhea (inhibit ovulation).
3. Endometriosis (long-lasting ovarian suppression).

Adverse Effects

1. Irregular bleeding followed by amenorrhea.
2. Depression.
3. Edema - hypertension - weight gain.
4. ↓ HDL.
5. Hirsutism, acne (androgenic).

Oral and Implantable Contraceptives

Mechanism of Action

1. Suppression of ovulation: inhibit FSH & LH.
2. Change cervical mucosa (thick & more acidic) → inhibit sperm penetration.
3. ↓ Endometrial glycogen deposition → inhibit implantation.

Types

A. Oral Preparations

1. Combined Preparations

Combination of estrogen and progestin (most effective).

2. Progestin-Only Preparations (Minipills)

Less reliable but no risk of thromboembolism.

B. Parenteral Progestin Preparations

a. Implants (norgestrel) →5 years.

b. Depot injections (medroxyprogesterone acetate) →3 months.

Indications

1. Contraception.
2. Regulation of menstrual cycle.

Adverse Effects & Contraindications (CI) of combined contraceptive pills

I. Minor Risks

1. Nausea, vomiting, headache.
2. Breast tenderness.
3. Edema.

II. Intermediate Risks

1. Bleeding (low dose), amenorrhea (large dose).
2. Acne, hirsutism, skin pigmentation.

III. Major Risks: mostly from estrogen. Modern preparations contain low-dose estrogen→↓ risks.

1. Cardiovascular: ↑ in females over 35 & smokers:
   a. Thromboembolism - pulmonary embolism.
   b. Hypertension - stroke - myocardial infarction.

CI: myocardial infarction and cerebrovascular disorders.

2. Carcinogenic[47]

↑ Risk of cervical?? & breast cancer (estrogen): ↓ by adding progestins.

CI:
1. Estrogen-dependent tumors of breast & uterus.
2. Undiagnosed vaginal bleeding.

3. Cholecystitis - gall stones – jaundice → **CI** in liver disease.
4. Depression: caused by progesterone.

Drug interactions

- Enzyme inducers: e.g. rifampicin →↓efficacy of oral contraceptives→ pregnancy.

---

[47] Combination oral contraceptives ↓ risk of ovarian cancer and endometrial cancer. This may be due to the progestin, which opposes estrogen-induced proliferation, throughout the entire 21 days.

Partial-Agonist Estrogens and Progestins

A. Selective estrogen receptor modifiers

1. Clomiphene

Mechanism of Action: Partial-agonist estrogen that acts centrally:

- Blocks **central estrogen receptors** in hypothalamus preventing normal feedback inhibition of estrogen on FSHRH & LHRH in hypothalamus → stimulation of ovulation and corpus luteum formation.

Uses (oral)

Ovulation inducing agent in infertility:

1. Female infertility due to disorders of ovulation.
2. with gonadotropins in "***in-vitro*** fertilization".

Adverse Effects

Hot flushes - multiple pregnancies - overstimulation of ovaries.

2. Tamoxifen

Mechanism of Action

Selective estrogen receptor modulator; partial agonist acting peripherally:

- **Antagonist**:

  Prevents endogenous estrogen from activating receptors in estrogen-sensitive breast cancer.

- **Agonist**:

  i. On bone: preserves bone mineral density (prevents osteoporosis in patients with breast cancer.

  ii. On uterus: increase incidence of endometrial cancer (<1%)

Use: treatment of hormone-sensitive breast cancer.

Adverse Effects: Hot flushes - vaginal discharges – menstrual irregularity.

3. Raloxifene

Mechanism:

- Selective estrogen receptor modulator (partial agonist), similar to estrogen on bone but not on breast or uterus → no risk of cancer.

Use :

- Treatment of osteoporosis

Side effects:

- Hot flashes – sweating.
- Leg cramps.

CI. History of venous thrombo-embolism.

B. Antiprogestins

Mifepristone **Danazole**

1. Mifepristone

Mechanism: competitive inhibitor of progesterone & glucocorticoid receptors[48].

Major use: Therapeutic abortion (e.g. in intrauterine fetal death).

2. Danazole[49]

Mechanism

- Weak androgen with anti-progestin and anti-estrogenic effects.
- Inhibits FSH and LH output → ↓ ovarian and testicular functions.

Uses[50]

1. Endometriosis.
2. Fibrocystic disease of breast.
3. Hereditary angioedema

Side Effects

1. Androgenic: acne - hirsutism.
2. Hypoestrogenic: flushing - sweating.
3. Amenorrhea, irregular menstruation.

Ovulation-Inducing Agents (in treatment of infertility)

1. Clomiphene.
2. Human chorionic gonadotropins.
3. Human menopausal gonadotropins: menotropins- urofollitropin
4. Gonadorelin (synthetic gonadotrophin releasing hormone): in sc pulses.
5. Bromocriptine: DA agonist → ↓ prolactin level in hyperprolactinemia.

---

[48] Mifepristone is also used in cushing syndrome.

[49] Danazole is a partial agonist at androgen, progestin & glucocorticoid receptors.

[50] Danazole is also used in inherited angioedema and haemophilia

Androgens

(Testosterone propionate – Methyltestosterone)

Actions

A. Androgenic: sex organs development, 2^{ry} sex characters, ⊕ spermatogenesis.

B. Anabolic: ↑ protein synthesis - ↑ bone & muscle development.

Uses: male hypogonadism.

Anabolic Steroids

(Stanozolol)

- Synthetic androgens with high anabolic and low androgenic activities.
- They promote tissue building processes (→ may be abused by atheletes).

Indications

1. Chronic debilitating diseases, e.g. cancer.
2. Osteoporosis: postmenopausal & in elderly males.
3. Prolonged immobilization.
4. To stimulate growth in boys with delayed puberty.

Adverse Effects

1. Virilization - acne in ♀; azospermia - ↑ libido in males.
2. Short stature in children (due to premature closure of epiphysis)
3. Cholestatic jaundice - cancer liver.

Antiandrogens

Finasteride

- Inhibitor of prostatic 5-α reductase that converts testosterone into active dihydrotestosterone→ used in **Prostatic Hyperplasia**.

Flutamide [51]

- Competitive inhibitors at androgen receptor.
- **Used in**: cancer prostate - excess androgenic effects in females (acne & hirsutism).

---

[51] Cyproterone is another antiandrogen used as flutamide & in hypersexuality in males. Bicalutamide is replacing flutamide as it is less hepatotoxic & is given once daily.

II. CHEMOTHERAPY

Intended Learning Outcomes (ILOs)

By the end of this chapter, the student should be able to recognize the following ILOs

General chemotherapy: the student should be able to

- Classify antimicrobials according to their mechanisms of action.
- Understand time- dependent & conc- dependent killing actions of antimicrobials.
- Recall the differences between different groups of penicillins.
- Recognize that penicillins are the safest antimicrobials except for the risk of hypersensitivity.
- Identify 2 major toxicities for each antimicrobial drug group.
- List some examples of nephrotoxic antimicrobials.
- List some examples of hepatotoxic antimicrobials.
- List some examples of drugs that should be avoided in children.
- Explain why clindamycin and broad spectrum antimicrobials may induce pseudomembraneous colitis.
- Discuss choices of antimicrobials for staph, anerobes, gram negative and gram positive infections.
- Recognize the fact that aminoglycosides are used parentrally in serious gram negative infections but not against anerobes.
- Recognize the difference in the shift of spectrum of newer generations of quinolones versus that of cephalosporins.
- Discuss clinically significant pharmacokinetic features of some antimicrobials, (e.g. renal elimination of aminoglycosides)and of individual members within the same group e.g. doxycycline versus other tetracyclines &ceftriaxone &cefoperazone versus other cephalosporins.
- Explain why the use of chloramphenicol is limited.
- List 3 special problems associated with antituberculous therapy.
- Explain the rationale behind combining penicillin with aminoglycosides, and sulfonamides with trimethoprim.
- List other beneficial antimicrobial combinations.

Special chemotherapy : the student should be able to

- Identify the mechanism of action , uses & adverse effects of metronidazole.
- Explain why chloroquine is given in amebic hepatitis.
- Explain why a luminal amebecide is given in all forms of amebiasis.
- Identify the target enzymes and choice of drugs in different viral infections.
- Classify antifungal drugs according to their indications in different fungal infections.
- Describe the mechanism of action of antifungal drugs.
- Recall the toxicity of amphotericin.
- Explain why flucytosine is combined with amphotericin.
- List the differences between ketoconazole and other azoles.
- Explain why nystatin is given orally and vaginally in candidal infection.

CHEMOTHERAPY

Chemotherapy includes:

1. **Antimicrobial Agents**
    - They include antibacterial, antifungal and antiviral drugs.
    - When derived from living organisms, they are termed "***Antibiotics***".
    - They are more selective on microorganisms with less toxic effects in human as they act on structures or chemical reactions specific to microorganisms.
2. **Antiparasitic Agents**
    - Anthelmintics and antiprotozoal drugs.
3. **Anticancer Chemotherapy**

ANTIBACTERIAL CHEMOTHERAPY

Classification of Antibacterial Drugs

A. Classification according to effect on bacteria:

- **Bactericidal:** kill the microorganisms & eradicate the infection with no need for the body defense mechanisms e.g. penicillins & aminoglycosides.
- **Bacteriostatic:** stop growth of microorganisms with the need for the body defense mechanisms to eradicate the infection e.g. tetracyclines & chloramphenicol.

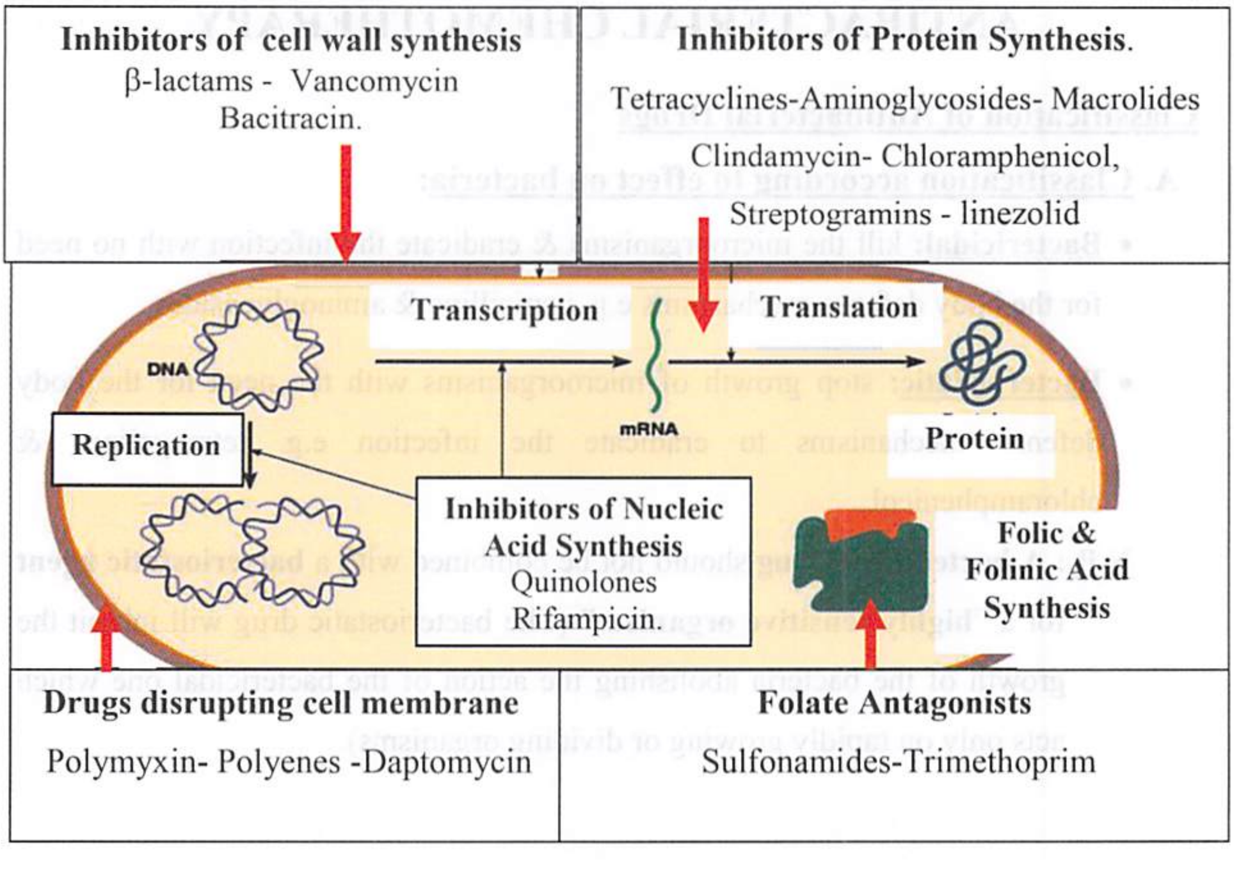
N.B.: A **bactericidal drug** should not be combined with a **bacteriostatic agent** for a "**highly sensitive organism**" (The bacteriostatic drug will inhibit the growth of the bacteria abolishing the action of the bactericidal one which acts only on rapidly growing or dividing organisms).

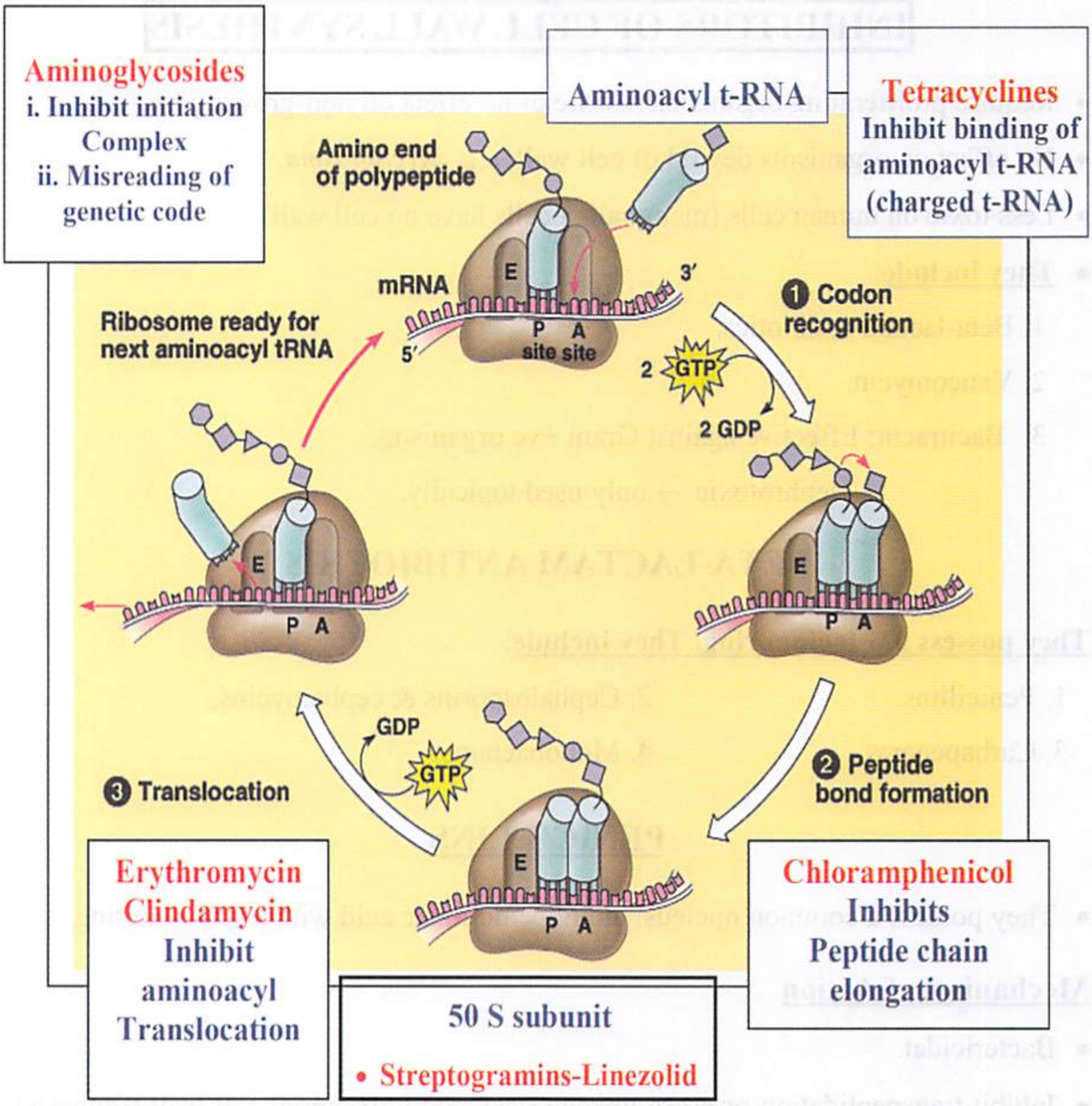
B. Classification according to antibacterial spectrum:

- **Broad-spectrum (on gram +ve & -ve)**, e.g. broad-spectrum penicillins, cephalosporins, tetracyclines, chloramphenicol, quinolones, co-trimoxazole.
- **Against Gram +ve organisms,** e.g. penicillin G, penicillinase-resistant penicillins, erythromycin, clindamycin, vancomycin, bacitracin, daptomycin, streptogramins & linezolid
- **Against Gram -ve organisms**, e.g. aminoglycosides & polymyxin.

C. Classification according to mechanism of Action:

1. Inhibitors of cell wall synthesis: e.g. β-lactams, vancomycin, bacitracin.
2. Inhibitors of protein synthesis: e.g. tetracyclines, aminoglycosides, macrolides, clindamycin, chloramphenicol, streptogramins & linezolid
3. Inhibitors of nucleic acid synthesis: e.g. quinolones, rifampicin.
4. Inhibitors of metabolic pathways: folate antagonists, e.g. sulfonamides, trimethoprim, co-trimoxazole (comb. of sulfonamides & trimethoprim).
5. Drugs disrupting cell membrane: e.g. polymyxin, polyenes, daptomycin.


Inhibitors of cell wall synthesis
β-lactams - Vancomycin
Bacitracin.
Inhibitors of Protein Synthesis.
Tetracyclines-Aminoglycosides- Macrolides
Clindamycin- Chloramphenicol,
Streptogramins - linezolid
Transcription
Translation
DNA
mRNA
Protein
Replication
Inhibitors of Nucleic Acid Synthesis
Quinolones
Rifampicin.
Folic & Folinic Acid Synthesis
Drugs disrupting cell membrane
Polymyxin- Polyenes -Daptomycin
Folate Antagonists
Sulfonamides-Trimethoprim


Aminoglycosides
i. Inhibit initiation Complex
ii. Misreading of genetic code
Aminoacyl t-RNA
Tetracyclines
Inhibit binding of aminoacyl t-RNA (charged t-RNA)
Amino end of polypeptide
mRNA
E
P
A
site site
3′
5′
Ribosome ready for next aminoacyl tRNA
① Codon recognition
2 GTP
2 GDP
② Peptide bond formation
GDP
GTP
③ Translocation
Erythromycin
Clindamycin
Inhibit aminoacyl Translocation
50 S subunit
• Streptogramins-Linezolid
Chloramphenicol
Inhibits Peptide chain elongation

Mechanism of Action of Antimicrobials Acting on Protein Synthesis

Steps of protein synthesis: To initiate translation, the m-RNA, transcribed from the DNA template is attached to the 30 s subunit of ribosome to which The 50 s subunit binds forming the 70 s subunit**.** This subunit moves along the m-RNA such that successive codons on the m-RNA pass along the ribosome from the A site to the P site. Reading of the genetic code on m-RNA is followed by:

Binding of t-RNA carrying the required amino acid to the A site on ribosome.

Transpeptidation: transfer of polypeptide on P site to bind with t-RNA on A site

Translocation: movement of ribosomes & translocation of polypeptide from A site to P site, leaving the A site empty for receiving a new t-RNA.

INHIBITORS OF CELL WALL SYNTHESIS

- Require proliferating organisms→ little or no effect on non-growing bacteria.
- No effect on organisms devoid of cell wall, e.g. *Mycoplasma*.
- Less toxic on human cells (mammalian cells have no cell wall).
- **They include**:
  1. Beta-lactam antibiotics.
  2. Vancomycin.
  3. Bacitracin: Effective against Gram +ve organisms.
     Nephrotoxic → only used topically.

BETA-LACTAM ANTIBIOTICS

They possess a β-lactam ring. They include:

1. Penicillins.
2. Cephalosporins & cephamycins.
3. Carbapenems.
4. Monobactams.

PENICILLINS

- They possess a common nucleus: aminopenicillanic acid with a β-lactam ring.

Mechanism of Action

- Bactericidal.
- Inhibit transpeptidation or cross-linkage (last step in bacterial cell wall synthesis), through binding to penicillin binding proteins (pbps[1]).
- ↑ Activity of autolysins produced by some bacteria leading to cell wall lysis.

β-Lactamase

- Enzyme secreted by some bacteria, e.g. *Staphylococci*, leading to inactivation of β-lactam antibiotics → resistance to these drugs.

---

[1] Both susceptible and resistant Gram -ve & Gram +ve organisms have pbps. Resistance of Gram -ve bacteria to narrow spectrum penicillins arises from presence of an outer membrane with pores too small to allow adequate penetration of the drug & access to the pbps.

Preparations of Penicillins

Due to different R groups attached to β-lactam ring, members of penicillins differ in:

- Spectrum.
- Stability to gastric acidity.
- Susceptibility to bacterial β-lactamase.

1. **Natural Penicillins [Penicillin G (benzylpenicillin) and Penicillin V].**
   - Narrow spectrum (Gram +ve cocci & bacilli) & Gram -ve cocci.
   - Penicillin V is acid-stable (so can be given orally).
   - Penicillin G is less stable to acid (so given parenterally).
   - Inactivated by β-lactamase.
2. **Anti-*Staph* Penicillins**[2]: e.g. oxacillin, cloxacillin, flucloxacillin & nafcillin.
   - Narrow spectrum as natural penicillins.
   - Stable to gastric acidity.
   - Stable to β-lactamase.
3. **Extended- -spectrum penicillins**, e.g. ampicillin & amoxicillin.
   - Broad-spectrum (as natural penicillins plus some Gram -ve bacilli).
   - Stable to gastric acidity (amoxicillin orally; ampicillin orally & parenterally).
   - Inactivated by β-lactamase.
4. **Antipseudomonal penicillins**[3], indanyl carbenicillin, piperacillin (most potent)
   - Broad-spectrum including Pseudomonas & many Gram-ve bacilli.
   - Indanyl carbenicillin is acid stable (oral); piperacillin is unstable (parenteral).
   - Inactivated by β-lactamase.

---

[2] Methicillin is the 1st preparation in this group. It is not used now due to its nephrotoxicity.

[3] Pseudomonas aeruginosa has restrictive porins, making this organism intrinsically resistant to many antimicrobial agents.

5. **Long acting penicillins**, e.g. benzathine penicillin - procaine penicillin
   - Insoluble salts of Penicillin G → allow slow drug absorption with long duration of action (penicillin G is short acting; 6 hours):
     - Procaine penicillin: given every 12 hours.
     - Benzathine penicillin: given once/ month.

N.B.:

- **Oxacillin** or **Methicillin Resistant Staph Aureus (ORSA** or **MRSA)** do not respond to other β-lactams because they acquire penicillin-binding proteins with low affinity for β-lactams (respond to vancomycin or rifampicin).

Routes of Administration

Depend on stability to gastric acidity & severity of infection:

1. **Oral**: in moderate infection and acid-stable preparations:
   e.g. Penicillin V & ampicillin.
2. **Parenteral** (IV or IM) in severe infections or acid-unstable preparations.
   - Penicillin G is preferred in severe infections with susceptible organisms.
   - Depot IM preparations: procaine penicillin (given/12-24 h), benzathine penicillin (long-acting given monthly as prophylactic against Rh. fever).

Advantages of Amoxicillin over Ampicillin

- Better absorption (almost completely absorbed).
- Higher plasma level.
- Less GIT disturbances & diarrhea.

Pharmacokinetics

Absorption

Most preparations are incompletely Absorbed orally, e.g. ampicillin.

Distribution

- Penicillins can cross placenta.
- Cross BBB when inflamed in case of meningitis.

Excretion

- Renal elimination (nafcillin & oxacillin, hepatic metabolism, biliary excreted).
- Probenecid inhibits renal tubular secretion of penicillin by competing with it for acid secretory mechanism. Thus, it prolongs penicillin action.

Therapeutic Uses

1. Streptococcal infections:
   - Acute throat infections, wound sepsis, puerperal fever.
   - Bacterial endocarditis: penicillin is given plus an aminoglycoside (facilitate penetration of aminoglycosides by interfering with bacterial cell wall synthesis →synergistic bactericidal effect).

2 separate IV bolus injections, to avoid interaction)

2. Staphylococcal infections.
3. Pneumococcal infections.
4. Syphilis & gonorrhea. (Alternative: fluorinated quinolones).
5. Meningococcal meningitis: penicillin G or ampicillin IV plus chloramphenicol.
6. Typhoid & paratyphoid fever: amoxicillin & ampicillin.
7. Diphtheria, tetanus & gas gangrene (penicillin **plus** specific antitoxins).
8. **Prophylaxis against**:
   a. Recurrence of rheumatic fever: benzathine penicillin (1.2 million units/month).
   b. Bacterial endocarditis (plus an aminoglycoside).

Adverse Effects (one of the safest antibiotics)

1. **Hypersensitivity** (most important): rashes & phlebitis (direct effect) or angioedema[4]& anaphylaxis (immunological due to antigenic metabolite penicilloic acid). Cross-allergy may occur between β-lactam antibiotics.
2. **Diarrhea:** due to disruption of normal balance of intestinal flora; more with incompletely absorbed & broad spectrum agents eg. ampicillin.
3. **Neurotoxicity:** seizures if injected intrathecally or with ↑ blood level.
4. **Cation disturbance**: K^+ in penicillin G → hyperkalemia.
5. **Decreased coagulation**: with high doses of piperacillin.

---

[4] Angioedema: marked swelling of lips, tongue, periorbital area.

CEPHALOSPORINS & CEPHAMYCINS

- β-Lactams: similar mechanism to penicillins but more resistant to β-lactamase.

Classification according to Antibacterial Spectrum

1st Generation (cephalexin, cefazolin)

Spectrum:

- G +ve cocci (Strept - Staph).
- Some G -ve organisms (E coli - Klebsiella).

Special features

- **Cephalexin**: oral, broad spectrum in upper respiratory & urinary infections.
- **Cefazolin** : 1st choice in surgical Prophylaxis & Orthopedic surgery:
  - Parentral
  - Penetrates bone well.
  - Penicillinase resistant (*Staph*).

2nd Generation (cefuroxime, cefaclor, cephamycins)

Spectrum:

- Less active on G +ve than 1st generation.
- Extended spectrum on G -ve organisms.
- Cephamycins: aerobic & **anerobic** G –ve bacilli.

Special features

- Oral agents are used in sinusititis - otitis.
- **Cefuroxime**: also used in community acquired pneumonia (H. influenza).
- **Cephamycins** (cefoxitin - cefotetan cefmetazole): structurally related to cephalosporins, parentral in mixed anerobic infections , B. fragillis, peritonitis.

3rd Generation (cefoperazone, cefotaxime, ceftriaxone, ceftazidime)

Spectrum: ↑ Activity against resistant G -ve organisms (e.g. Pseudomonas).

Special features:

- Used in serious infections.
- Most agents can cross BBB (used in meningitis)

Ceftriaxone (Parenteral , longest $t_{½}$.)

- Used in gonorrhea (single injection) - typhoid (resistant cases).
- Bone: good penetration into bone.
- **BBB**: crosses BBB, so can be used in meningitis.
- Bile: excreted in bile (40%), used in biliary infection & in renal dysfunction.

4th Generation (Cefepime; parentral)

- Similar spectrum to 3rd gen. on gram negative & crosses BBB well.
- Effective on penicillin resistant streptococci & staphylococci.

5th Generation (Ceftarolene fosamil)

- Broad spectrum pro-drug of active metabolite ceftarolene.
- **Sectrum:** MRSA, VRSA, H influenza, gram negative (plus amino glycosides).
- Used in: skin infections and community acquired pneumonia.
- Requires dose adjustment in renal impairment.

Pharmacokinetics

- Some members are absorbed orally but most are given parentrally.
- Agents of 1st & 2nd generations cannot cross BBB while 3rd-generation agents (except cefoperazone) can cross → useful in meningitis.
- Elimination is mainly renal → adjust dose in renal dysfunction.
- Cefoperazone & ceftriaxone are excreted mainly in bile[5] → can be used in biliary infection & patients with renal dysfunction.

Adverse effects

1. Hypersensitivity: avoid in pts with serious penicillin allergy (cross-allergy).
2. Nephrotoxicity especially if used with aminoglycosides.
3. Local irritation → severe pain after IMI and thrombophlebitis after IVI.
4. Hypoprothrombinemia & bleeding (cefoperazone).
5. Intolerance to alcohol → disulfiram-like reaction.
6. Cross-resistance with penicillins: avoided in penicillin- resistant infections.

---

[5] Cefoperazone (75 %) & ceftriaxone (40 %) are excreted in bile

Other β-Lactam Antibiotics

CARBAPENEMS

Imipenem

(Given IV)

- Broadest-spectrum β-lactams.
- Effective against Gram +ve, -ve organisms and **anaerobes.**
- Resistant to β-lactamase.
- ↑↑↑cross-allergy with penicillin
- **↑ Risk of Toxicity:**
  1. Metabolized in kidney to an inactive nephrotoxic metabolite →has to be given with cilastatin to inhibit renal metabolism.
  2. ↑ risk of convulsion → **avoided in meningitis**

MONOBACTAMS

Aztreonam

(Given IV & IM)

- Narrow spectrum.
- Effective against aerobic gram -ve organisms (as aminoglycosides).
- Resistant to β-lactamase.
- No cross-allergy with β-lactams.
- **Relatively non-toxic:**
  - Similar to β-lactams with less risk of hypersensitivity.

Meropenem & Ertapenem

- Similar to imipenem with less renal degradation (cilastatin is not required) &↓ risk of convulsions.

β-Lactamase Inhibitors: Clavulanic acid & Sulbactam

- They do not have significant antibacterial effect.
- *Irreversibly* inhibit β-lactamase, → protect antibiotics inactivated by it.
- Combined with β-lactam antibiotics for β-lactamase-producing organisms.:
  - Amoxicillin + clavulanic acid (Augmentin)
  - Ampicillin + sulbactam (Unasyn)
  - Cefoperazone + sulbactam (Sulperazone)
  - Piperacillin + tazobactam (Zosyn)

VANCOMYCIN

Mechanism of Action (Bactericidal)

- Inhibits cell wall synthesis at an earlier stage than β-lactam antibiotics.

Uses (Gram +ve organisms)

1. *Staph* resistant to penicillin (ORSA or MRSA): **drug of choice: used in** Serious infections as Staph pneumonia, endocarditis & osteomyelitis.
2. Severe staph infections in patients allergic to penicillins or cephalosporins.
3. Pseudomembraneous colitis following antibiotic use, e.g. clindamycin.

Pharmacokinetics

- Given by IV infusion.
- Given orally in antibiotic-induced pseudomembraneous colitis due to Clostridium difficile (not well absorbed; acts locally).
- Excreted renally: dose adjustment is required in renal dysfunction.

Adverse effects

1. Fever, chills, rigors and phlebitis.
2. Shock with rapid infusion → **red man syndrome** (due to histamine release), avoided by slow infusion & pretreatment with antihistamines.
3. Ototoxic.
4. Nephrotoxic.

Drug-induced Pseudomemberaneous Colitis:

- **Clindamycin.**
- **Broad-spectrum antimicrobials**

Tetracyclines, co-trimoxazole, chloramphenicol

→ Kill intestinal flora → flourishing of *Clostridium difficile* (G +ve anerobe) & its toxins → colitis.

Treatment

1. Metronidazole or vancomycin.
2. Cholestyramine to bind toxins.

TELAVANCIN (synthetic derivative of vancomycin)

Mechanism of action (bactericidal)

- Inhibits bacterial cell wall synthesis.
- Disruption of cell membrane.

Spectrum (gram positive)

- MRSA,VRSA, daptomycin & linezolid resistant infections.

Adverse effects

1. Metallic taste.
2. **Red man syndrome**, allergy.
3. Nephrotoxic.
4. Prolongs QT interval.

TEICOPLANIN

- Similar to vancomycin in mechanism, spectrum & renal elimination.
- Has the advantage of once daily administration by IM as well as IV routes.

ANTIMICROBIALS DISRUPTING CELL MEMBRANES

DAPTOMYCIN

Mechanism of action

- Binds to & depolarizes cell membrane causing rapid cell death.

Spectrum

- Similar to vancomycin on Gram +ve organisms

Advantages

- More rapidly bactericidal.
- Effective against vancomycin resistant organisms.

Uses (IV & IM)

1. Skin & soft tissue infections
2. Bacteremia & endocarditis.

Adverse effects

1. GIT upset & elevated liver enzymes.
2. Myopathy → avoid with statins.

N.B.: Daptomycin is inactivated by pulmonary surfactants; **CI** in pneumonia.

INHIBITORS OF PROTEIN SYNTHESIS

- Tetracyclines
- Macrolides
- Aminoglycosides
- Clindamycin
- Chloramphenicol

TETRACYCLINES

Members

- Tetracycline: short acting.
- Demeclocycline: intermediate
- Doxycycline
- Minocycline

Doxycycline, Minocycline } → Long-acting (Lipophilic); given once /d

Mechanism of Action (Bacteriostatic)

- Bind to 30S ribosomal bacterial subunits → inhibition of binding of tRNA → inhibition of protein synthesis.

Spectrum & Uses

1. Tetracyclines are broad-spectrum antibiotics used in:
    - Amebiasis - Acne.
    - Brucellosis - Biliary infection (doxycycline & minocycline).
    - Chlamydial infections - Cholera (doxycycline + fluid replacement).
    - Mycoplasma pneumonia - Meningococcal carriers (Minocycline; conc. in saliva).
    - Rickettsial infection.
2. Demeclocycline is used in treatment of Syndrome of Inappropriate Secretion of Antidiuretic Hormone (by antagonizing effect of ADH on renal tubules).

Pharmacokinetics

Absorption

- Incomplete oral absorption.

> Absorption is decreased by food due to formation of non-absorbable chelates of tetracycline with Ca^{2+}, Mg^{2+}, Al^{3+} (in antacids) and iron.

Distribution

- Penetrate BBB in insufficient concentration for therapeutic effect.

> - Tetracyclines are concentrated in bone & teeth → deformities.
> - Tetracyclines can cross the placenta and affect fetal bones.

Metabolism & Excretion

- Metabolized in part in liver & metabolites & parent drug are excreted in bile, undergo enterohepatic circulation (especially doxycycline).
- Excreted in urine (↑ $t_{1/2}$ in renal dysfunction)→ **CI in renal dysfunction** except **doxycycline** which is eliminated mainly in bile

Adverse Effects & Contraindications

1. Epigastric pain due to gastric irritation (non-compliance) →↓if taken with non-dairy food (to avoid chelation with Ca^{2+} in milk).
2. Teeth discoloration & bone hypoplasia→**CI**: pregnancy, lactation & child < 8 y.
3. Hepatotoxicity (in renal failure or pregnancy).
4. Phototoxicity (sensitivity of skin to sun light).
5. Superinfection with *Candida, C. difficile* or resistant *Staph* in intestine.
6. Fanconi-like syndrome: renal tubular dysfunction with outdated tetracyclines.
7. Contraindicated in renal dysfunction.

TIGECYCLINE

- Similar to tetracycline in mechanism of action & adverse effects (structurally similar).
- Effective against gram positive, gram negative & anerobes
- Given by slow iv infusion (adjust dose in liver impairment).

AMINOGLYCOSIDES

Members

- Streptomycin
- Gentamycin
- Tobramycin
- Amikacin
- Netilmicin
- Neomycin

Mechanism of Action (Bactericidal)

Irreversibly bind with 30S ribosomal bacterial subunits leading to inhibition of protein synthesis by:

- Inhibition of formation of the initiation complex.
- Misreading of mRNA leading to formation of abnormal protein.
- Breaking down of polysomes to nonfunctional monosomes.

Spectrum and Activity

- Effective against aerobic organisms.
- Ineffective against anaerobes (requires O_2 for transport into cells).
- Act mainly against Gram -ve organisms, e.g. *E-coli*, *Pseudomonas*, cholera.
- Gentamycin is also effective against *Staph* infections.
- Amikacin resists bacterial enzymatic inactivation, thus it is the most effective aminoglycoside against Gram -ve bacilli.

Pharmacokinetics

Absorption

- Not absorbed orally thus have to be given parenterally.

Distribution

- They do not cross BBB even when meninges are inflamed.
- Aminoglycosides are concentrated in renal cortex, perilymph & endolymph of inner ear → nephrotoxicity & ototoxicity.

Excretion

- Aminoglycosides are excreted unchanged through the kidney, so precaution should be taken in patients with renal dysfunction.

Adverse Effects

1. **Nephrotoxicity**

   Acute tubular necrosis (may be irreversible). Risk ↑ by dehydration, old age, ↑ dose, ↑ treatment duration or concurrent use of nephrotoxic drugs.

2. **Ototoxicity**

   May be irreversible. Coadministration of loop diuretics or quinidine →↑ risk.

3. **Neuromuscular paralysis** (inhibits Ach release)

   Especially after intraperitoneal or intrapleural infusion of large doses ().

4. **Allergy**

   Contact dermatitis with topically applied neomycin.

Therapeutic Uses (toxic, reserved for serious infections, plus penicillins)

1. Peritonitis, septicemia, pneumonia.
2. Bacterial endocarditis.
3. Complicated urinary tract infection.
4. **Streptomycin** is used in TB.
5. **Amikacin & netilmicin** are reserved for resistant cases.
6. **Neomycin** (too nephrotoxic for systemic use): used **orally** in hepatic coma & intestinal antiseptic before surgery (not absorbed) & **topically** in infected wounds.

Spectinomycin: (structurally related to aminoglycosides)

- It inhibits protein synthesis at 30 S subunit.
- Its use is limited to gonorrhea in patients allergic to penicillin or patients with penicillin-resistant gonococcal infection (single deep IMI).

MACROLIDES

Members

- Erythromycin
- Clarithromycin
- Azithromycin
- Roxithromycin.

New members

Semisynthetic derivatives of erythromycin

Erythromycin

Mechanism of Action (Bacteriostatic)

- Binds to 50S ribosomal subunits preventing translocation →inhibition of protein synthesis (**bacteriostatic** at low conc & **bactericidal** at high conc).

Spectrum & Uses

- Chlamydia, Mycoplasma, Spirochetes, Gram +ve cocci & bacilli as an alternative to penicillins & tetracyclines: **Drug of choice for**
  - Patients with allergy to β-lactam antibiotics.
  - Urogenital Chlamydia infection in pregnancy.
  - Mycoplasma pneumonia in children (tetracyclines are contraindicated).

Pharmacokinetics

- Erythromycin is destroyed by gastric acidity, so given as enteric-coated tablets, stable salts or esters (clarithromycin is not destroyed by gastric acidity).
- Food decreases absorption of erythromycin, but ↑ clarithromycin absorption.
- Poor penetration to CNS.
- Metabolized in liver & inhibits oxidation of other drugs (**enzyme inhibitor**).

Adverse Effects

1. Epigastric pain & GIT distress (increases bowel motility).
2. Cholestatic jaundice (erythromycin estolate). **CI:** in liver disease.
3. Ototoxicity and may lead to transient deafness.
4. Thrombophlebitis if injected intravenously (erythromycin).
5. Prolongation of QT interval.

Drug Interactions

1. Enzyme inhibitor: ↑ level of theophylline, warfarin, carbamazepine.
2. ↑ digoxin level (inhibits intestinal flora that inactivate digoxin).

Advantages of new generation macrolides over erythromycin :

a. Gastric acid stability.

b. Better absorption.

c. Long $t_{½}$.

Azithromycin

- Less effective on Gram +ve, more effective on Gram -ve micro-organisms than erythromycin.
- Potent against *Chlamydia.*
- Long $t_{½}$, allowing once-daily dosing.
- Excreted through bile.

Clindamycin

- Similar to macrolides (bacteriostatic).
- It is used specifically against **anaerobic infections.**
- It is effective against Gram +ve organisms: *Staph* & *Strept* infections.
- It is used in bone infection (good penetration into bone).

Adverse Effects

1. **Pseudomembraneous colitis.**
2. Skin rash.
3. Diarrhea.
4. Liver dysfunction.

CHLORAMPHENICOL

Mechanism of Action (Bacteriostatic)

- It binds with 50S ribosomal subunits inhibiting transpeptidation → inhibiting peptide chain elongation →inhibition of protein synthesis.

Spectrum

- It is a broad-spectrum drug (affecting bacteria & rickettsia).

Uses of Chloramphenicol

- Because of its toxicity, its use is restricted to:
  1. Typhoid fever (not carrier), but replaced by fl. quinolones.
  2. Bacterial meningitis (e.g. *H. influenza*) plus penicillin.
  3. Topically in eye infections.
  4. Anaerobic infection, e.g. anaerobic brain abscess.

Pharmacokinetics

1. It is completely absorbed orally.
2. Distributed all over the body reaching the CSF.
3. Metabolized in liver. It inhibits microsomal enzymes.
4. Excreted via kidney.

Adverse Effects

1. GIT upsets and superinfection.
2. **Bone marrow depression**: may be dose-independent or idiosyncratic.
3. **Grey baby syndrome** in neonates (↓ drug clearance due to undeveloped liver & kidney functions).
4. Optic neuritis.
5. Enzyme inhibitor : ↑ warfarin, phenytoin & oral hypoglycemics level.

STREPTOGRAMINS

Quinupristin / Dalfopristin[6]

Mechanism of Action

- Complex with bacterial 50S ribosomal subunits to inhibit protein synthesis

Spectrum & Uses (iv infusion)

- Serious infections with resistant Gram +ve organisms e.g. MRSA & streptococcus pneumonia when vancomycin cannot be tolerated

Adverse Effects

1. Arthralgia & myalgia.
2. Thrombophlebitis.
3. Enzyme inhibitor → drug interactions (similar to erythromycin)

OXAZOLIDINONES

Linezolid

Mechanism of Action

- Binds to a unique site on 50S subunit → inhibits initiation complex & protein synthesis.

Spectrum & Uses (iv = oral[7])

- Restricted to serious G +ve infections resistant to vancomycin or MRSA in patients intolerant to vancomycin or if iv access is unavailable.

Adverse Effects

1. Thrombocytopenia.
2. GIT: Nausea, vomiting & diarrhea.
3. Mild MAOI→ avoid with SSRIs & pseudoephedrine in cold remedies →↑ BP

---

[6] Given in combination as they are less active if given separately: 7.5 mg/Kg every 8-12hrs.

[7] 100% bioavailability: 600mg twice daily oral or iv

INHIBITORS OF NUCLEIC ACID SYNTHESIS

Quinolones

Rifampicin

QUINOLONES

Mechanism of Action (Bactericidal)

- Inhibit **DNA gyrase (topoisomerase II)** enzyme, which is responsible for unwinding of double-stranded DNA leading to inhibition of DNA replication.
- Also inhibits topoisomerase IV responsible for cell division.

Classification

I. Nonfluorinated Quinolones **1^{ST} Generation**	**II. Fluorinated Quinolones** **2nd → 4th Generation**
Nalidixic Acid • Not used in systemic infections 90% of drug is bound to plasma proteins → insufficient plasma conc. • Was used only in urinary tract infections with G-ve bacilli. • Rapid resistance limits its use.	Newer Fluorinated derivatives achieving systemic levels ↓ Used in Systemic Infections

II. Generations of Flouroquinolones

- Fl.quinolones were effective mainly against aerobic G -ve organisms , weak against G +ve & ineffective against anerobes.
- Newer generations have ↑activity on Gram +ve cocci & anerobes.

2nd Generation: norfloxacin - ciprofloxacin – ofloxacin – pefloxacin

- **Excellent on Gram-ve**: pseudomonas, E. coli, H. influenza, proteus, salmonella & penicillinase-producing gonococci (ciprofloxacin is superior to all specially against pseudomonas).
- **Moderate on G+ve:** staph (not MRSA), weak on strepto- & pneumo-cocci.

N.B.: Norfloxacin is used in urinary tract infections only as it does not achieve systemic levels.

3rd Generation: Levofloxacin

- Effective against G-ve organisms.
- Greater effect on G +ve (pneumococci) than ciprofloxacin.

4th Generation: Moxifloxacin - Clinafloxacin

- Gram-ve activity < ciprofloxacin (poor against pseudomonas).
- Improved activity against G +ve cocci esp. S pneumonia & some staph.
- Active against anerobes (clinafloxacin most potent).

Uses of quinolones

1. Typhoid & infective diarrhea (ciprofloxacin: 1st choice for empiric therapy).
2. Active against **anerobes** (clinafloxacin: the most potent).
3. Urinary tract infections (Gram –ve bacilli) & prostatitis.
4. Gonorrhea (ofloxacin single dose, levofloxacin[8]).
5. Respiratory infections resistant to β-lactams & atypical pneumonia due to chlamydia, mycoplasma, legionella (levofloxacin- moxifloxacin).
6. Bone & soft tissue infection.
7. Resistant TB.

---

[8] Derivative of ofloxacin replaced it in treatment of gonorrhea

Adverse Effects and Contraindications (CI)

1. GIT: Nausea, vomiting & diarrhea (most common).
2. CNS: Headache, dizziness, insomnia, convulsions in susceptible patients.
3. Phototoxicity.
4. Hepatotoxicity .
5. Reversible arthropathy (children < 18 years).
6. **Drug interactions**
   - a. Enzyme inhibitor → ↑ serum level of theophylline, warfarin and cyclosporin (ciprofloxacin).
   - b.↑QT interval → arrhythmias (↑risk with hypokalemia & with drugs that ↑ QT interval e.g., erythromycin, class IA & III antiarrhythmics & TCAs.
   - c. Cations (in antacids) →↓ absorption of quinolones.

- Quinolones are **contraindicated** in pregnancy & lactation.
- Not routinely recommended in patients <18 years (→arthropathy).

RIFAMPICIN (Rifampin)

Mechanism:

- Binds & inhibits DNA-dependent RNA polymerase → inhibits RNA synthesis.

Antimicrobial spectrum:

- Potent broad spectrum bactericidal. Effective against ORSA (or MRSA).
- Effective against mycobacteria at all sites & leprosy.
- Antiviral effect.

Kinetics:

- Well absorbed after oral administration.
- Widely distributed in body tissues & fluids & can reach TB cavities & sputum & penetrate macrophages killing slowly growing TB bacilli inside.
- Crosses BBB.
- Metabolized in the liver & it is a potent enzyme inducer.
- Excreted mainly in bile (enterohepatic recycling) & slightly in urine.

Uses:

1. Mycobacteria: TB (**main use**), leprosy.
2. Meningitis Prophylaxis.
3. MRSA (ORSA).
4. Brucellosis; plus doxycycline (1st **choice**).

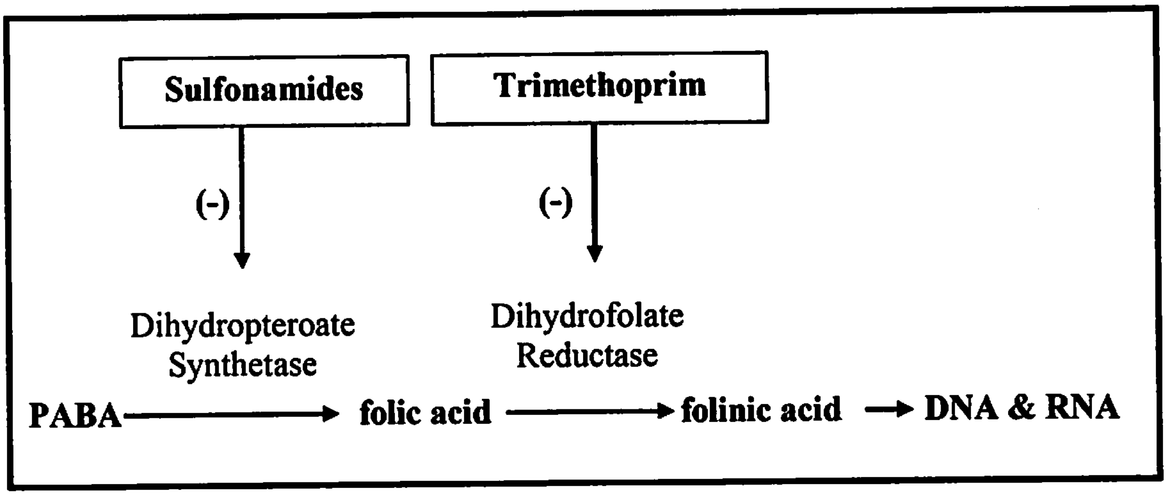
Adverse effects:

1. Skin rash, fever and GIT upset (Most common).
2. Liver damage and jaundice.
3. **Enzyme induction** (serious drug interactions); rifabutin is a less potent enzyme inducer thus induces less drug interaction.
4. An influenza-like syndrome (malaise, headache and fever, ..).
5. Red discoloration of urine, tears, sputum and soft contact lenses.
6. Resistance[9]: rapid (but no cross resistance with other anti-TB drugs).

---

[9] Due to modification of DNA-dependent RNA polymerase by chromosomal mutation

FOLATE-ANTAGONISTS


Sulfonamides
Trimethoprim
(-)
(-)
Dihydropteroate Synthetase
Dihydrofolate Reductase
PABA
folic acid
folinic acid
DNA & RNA

SULFONAMIDES

Members

- Sulfadiazine - sulfamethoxazole - sulfadoxine.
- Sulfacetamide (topical eye preparation).

Mechanism of Action (Bacteriostatic)

- Sulfonamides are structural analogs of PABA→compete with it for dihydropteroate synthetase → inhibition of folate synthesis→ inhibition of DNA & RNA synthesis.

N.B.: Human cells utilize already-formed folic acid (explains selectivity of sulfonamides to bacteria).

Therapeutic Uses

1. **Antibacterial**: Sulfamethoxazole + trimethoprim (Co-trimoxazole).
2. **Eye infections**: topical sulfacetamide.
3. **Burns**: topical silver sulfadiazine.
4. **Ulcerative colitis**: sulfasalazine.
5. **Malaria:** sulfadoxine + pyrimethamine (Fansidar).

Adverse Effects

1. **Crystalluria & nephrotoxicity**
   - ☐ Sulfonamides metabolites formed in liver precipitate in acidic urine → crystalluria & nephritis (avoid by ↑ fluid intake & urine alkalinization).
2. **Hypersensitivity reactions.**
3. **Hematopoietic disturbances.**
   - ☐ Granulocytopenia & thrombocytopenia
   - ☐ Hemolytic anemia in patients with G-6-PD deficiency.
4. **Kernicterus** (Jaundice & CNS affection)
   - ☐ Displace bilirubin from plasma protein. Free bilirubin crosses BBB (immature in newly-born) & reaches CNS.
5. **Interactions**
   - ☐ ↑ level of oral hypoglycemics & anticoagulants (displacement from plasma proteis).

TRIMETHOPRIM

Mechanism of Action

- Inhibition of dihydrofolate reductase enzyme, which converts folic acid to tetrahydrofolic acid (folinic acid), which is essential for DNA synthesis.

Adverse Effects

1. Megaloblastic anemia (folate deficiency).
2. Granulocytopenia & leucopoenia.

CO-TRIMOXAZOLE

- It is a combination of: sulfamethoxazole (400 mg) + trimethoprim (80 mg).

Mechanism of Action

- See sulfonamides & trimethoprim.

Advantages

1. Synergistic combination.
2. Less and delayed bacterial resistance
3. More potent (Bactericidal) & wider-spectrum including Proteus, Salmonella, Shigella, H. influenza & Gonococcus.

Therapeutic Uses

1. Urinary tract infections, gonococcal urethritis and prostatitis.
2. *Salmonella & Shigella* infections.
3. Respiratory tract infection due to *H. influenza & S. pneumonia.*
4. MRSA

Adverse Effects

- See sulfonamides and trimethoprim

Urinary antiseptics: for urinary tract infections (UTI)

- UTI (E coli & staph) are treated with antimicrobials & urinary antiseptics, including:

Nitrofurantoin

Mechanism : reduced by bacteria to a highly active intermediate→ DNA damage.

Spectrum: E coli & staphylococci.

Adverse Effects: GIT upset- neurological disturbances – acute pneumonitis & fibrosis

Methenamine

Mechanism : decomposes in acidic urine to formaldehyde→toxic to bacteria.

Uses: chonic suppressive therapy to reduce frequency of urinary tract infections.

Adverse Effects: GIT upset- albuminuria, hematuria, and rash.

ANTI-TUBERCULOUS DRUGS

- TB bacilli grow slowly.They are intracellular (inactive), extracellular (active) or present in necrotic TB tissues.

Problems with TB therapy:

1. Emergence of resistant bacilli as the organisms grow slowly, so combination of drugs is required.
2. Slowly growing organisms → disease has to be treated for a long period (minimum of 6 months up to 2 years) to prevent relapse.
3. Poor compliance when multidrug therapy lasts for 6 months or more → to ensure completion of therapy use "directly observed therapy" (**DOT**) in which patients take drugs under supervision & observation.

Anti-TB drugs include:

I. 1ST line drugs (↑efficacy, accepted degree of toxicity):

1. **Rifampicin**: affects the organisms at all sites.
2. **Isoniazid (INH):** affects intracellular & extracellular organisms.
3. **Pyrazinamide**:affects mainly intracellular organisms(resistant strains).
4. **Ethambutol.**

II. 2nd line drugs (used in resistance/ intolerance to 1st line drugs)[10]:

1. **Streptomycin**: affects only the extracelular organisms.
2. **Ceftriaxone.**
3. **Fluoroquinolones** (ciprofloxacin, levofloxacin & moxifloxacin).
4. **Cycloserine** → peripheral neuritis & CNS dysfunction.
5. **Ethionamide** →peripheral & optic neuritis
6. **Capreomycin** → nephrotoxic & ototoxic.
7. **Clarithromycin.**

---

[10] Other second line drugs: **aminosalicylic acid.**

General principles for treatment of TB

1. Bactericidal drugs are preferred.
2. Treatment involves 2 **phases** :
   - a- **Initial intensive phase:** For 2 months
     - 4 drugs are used to ↓ the number of bacilli to avoid resistance.
     - **Drugs used:** Rifampicin + INH + pyrazinamide + ethambutol or streptomycin.
   - b- **Continuation phase**: minimum of 4 months.
     - 2 drugs are used: INH & rifampicin.

INDIVIDUAL DRUGS

I. ISONIAZID (INH)

Mechanism of action:

- Affects the enzyme responsible for assembly of mycolic acid in mycobacteria cell wall (unique structure).

Pharmacokinetics:

- Readily absorbed from GIT & widely distributed into all body tissues and fluids (CSF, pleural and ascitic fluids, sputum, saliva, and caseous tissue).
- Metabolized in the liver mainly by acetylation which is genetically determined; individuals are either rapid or slow acetylators[11] (respond better).

Adverse effects

1. Hypersensitivity.
2. Neurotoxicity with slow acetylators (B6 deficiency[12]): peripheral neuritis, optic neuritis, memory impairment & convulsions → Vit. B_6 supplements.
3. Hepatitis: rare but fatal, risk is increased with age.
4. Enzyme inhibitor: ↑phenytoin & carbamazepine serum level.

---

[11] $T_{1/2}$ is one hour with rapid & 3 hours with slow acetylators.

[12] INH metabolites inhibit pyridoxine phosphokinase, which converts pyridoxine (B-6) to active form, which is required for GABA synthesis. INH overdose→↓pyridoxal-5-phosphate & ↓GABA→ CNS stimulation

II- RIFAMPICIN: see before

III- PYRAZINAMIDE

- **Mechanism** : the drug targets mycobacterial fatty acid synthase -I gene involved in mycolic acid synthesis.
- Bactericidal against resistant intracellular bacilli.
- Given orally, penetrates CSF→ valuable in tuberculous meningitis
- Resistance develops rapidly.
- **Adverse effects**: hepatitis - hyperuricemia & arthralgia - GIT upset.

IV- ETHAMBUTOL

- Bacteriostatic; enters active mycobacteria→ inhibit RNA synthesis.

Side effects:

- Optic neuritis → red/green colour blindness - ↓visual acuity.

Antileprotic Drugs

Management:

Drug combinations are used to ↓resistance:

- Paucibacillary[13] leprosy : dapsone + rifampicin (for 6 months).
- Multibacillary leprosy: dapsone + rifampicin + clofazimine (for 2 years).

I. Rifampicin: the most active agent (see before)

II. Dapsone

- A bacteriostatic related to sulfonamides achieves high skin concentration.
- Antagonist to PABA→ inhibits folate synthesis.

Adverse effects:

1. Hemolysis (esp. in G-6-PD def.) - methemoglobuinemia.
2. Peripheral neuropathy.
3. Erythema nodosum leprosum → suppressed by corticosteroids.

III. Clofazimine (oral)

- A dye accumulating in phagocytes & skin → bactericidal effect through:
  - Binding to DNA, preventing template formation & DNA replication.
  - Formation of cytotoxic oxygen radicals.
- Anti-inflammatory: used in patients developing erythema nodosum leprosum with dapsone.

Adverse effects:

- Skin discoloration (red - brown).
- Enteritis.

---

[13] Paucibacillary = few bacilli.

CLINICAL ASPECTS OF ANTIMICROBIALS

- **Empirical therapy**: It is the use of antimicrobial agents before identification of causative organism or availability of susceptibility test results.
- **Definitive therapy**: It involves the use of antimicrobial agent after identification/susceptibility tests of causative organism responsible for the disease.
- In severe infections, empirical therapy with antimicrobial drug combination should be initiated depending on the clinical diagnosis. Later, the antimicrobial agent should be selected according to the type of organism, culture and sensitivity reports.
- Bacterial resistance to antimicrobial agent and cross-resistance should also be considered while selecting drugs.

Antibiotic Pharmacodynamic Categories

I. **Conc. –Dependent** With Post antibiotic effect	II. **Time- Dependent** With minimal or no Post antibiotic effect	III. **Time-Dependent** With enhanced Post antibiotic effect
• Aminoglycosides • Quinolones	• β-lactams • Vancomycin	• Erythromycin • Tetracycline • Clindamycin • Streptogramins • linezolid

N.B.: post antibiotic effect (PAE): persistence of antibiotic effect for a period of time after its level falls below the minimum inhibitory concentration (MIC).

I. Concentration –Dependent antibiotics with PAE:

- Bactericidal effect depends on **drug concentration** (increased effect with increased concentration).
- Optimum effect is achieved with concentration 10 times MIC.
- Trough drug conc. may fall below MIC during dosing interval without loss of efficacy as bacterial regrowth is inhibited by the PAE→↓resistance

Maximize drug Conc

- Large infrequent doses are as effective as small frequent doses & may be less toxic.

II. Time- Dependent antibiotics with Minimal/ no PAE :

- Bactericidal effect depends on the **duration** during which the drug level exceeds MIC[14].
- Concentrations should be maintained at 2 to 4 times MIC throughout the dosing interval as bacterial re-growth starts very soon after trough falls below MIC since drug has no PAE.

Maximize duration of exposure to drug

- Small frequent doses & IV infusions are superior to large infrequent doses.

III. Time-Dependent Antibiotics with enhanced PAE:

- Drugs have both time -dependent & concentration – dependent effects.

---

[14] Time above MIC(T> MIC) is an important parameter

Antimicrobial Drug Combinations

Indications

1. To provide broad spectrum empirical therapy in severely ill patient.
2. To treat polymicrobial infection such as intra-abdominal abscess.
3. To ↓ development of resistant strains e.g. in cases of TB infection.
4. To ↓ dose-related toxicity by reducing doses of one or more of the combined drugs.
5. To obtain enhanced inhibition or killing (**Synergism**).

Examples of useful combinations & their mechanisms

1. Penicillins + aminoglycosides in bacterial endocarditis (**↑ antimicrobial effect & aminoglycosides uptake**).
2. Augmentin = Amoxacillin + clavulanic acid (β-lactamase inhibitor) (**Inhibition of enzymatic inactivation**).
3. Co-trimoxazole = Sulfamethoxazole + trimethoprim (**Blockade of sequential steps in a metabolic sequence**).
4. Anti-TB drugs e.g. INH + rifampicin + ethambutol or pyrazinamide (↓ resistance)

Disadvantages of unnecessary use of antimicrobial combinations

1. ↑ Toxicity .

2. ↑Cost.

3. May ↓ efficacy due to **antagonism**:

- Inhibition of bactericidal activity by bacteristatic drugs (tetracycline →↓penicillin efficacy).
- Induction of enzymatic inactivation e.g. β-lactams (imipenem, cefoxitin & ampicillin) are potent inducers of β-lactamase.

4. Increased risk of superinfection.

5, Irrational combination can lead to development of resistance.

Choice of Antimicrobials

❖ Antimicrobials against penicillinase-producing *Staph.*

- Antistaph penicillins: e.g., cloxacillin, cloxacillin, nafcillin.............. or amoxicillin + clavulanic acid.
- Cephalosporins: cephalexin, cefazolin, cefuroxime.
- Clindamycin - Co-trimoxazole

❖ Antimicrobials against ORSA (or MRSA):

- Vancomycin & Rifampicin.
- Daptomycin (if resistant to vancomycin & can be given IM).
- Quinupristin / Dalfopristin (if resistant to vancomycin (VRSA).
- Linezolid (if resistant to vancomycin (VRSA); can be given orally).
- Telavancin (MRSA & VRSA, daptomycin & linezolid resistant cases).
- Ceftarolene fosamil (MRSA & VRSA).
- Co-trimoxazole.

❖ Antimicrobials against gram negative organisms:

- Anti-psuedomonas penicillins, e.g., piperacillin+tazobactam ......
- Cephalosporins: ceftazidime, cefepime.
- Quinolones: ciprofloxacin.
- Meropinem.
- Aminoglycosides (combined with other agents in the immuno-compromized).

❖ Antimicrobials for anaerobic infections:

- Metronidazole.
- Clindamycin
- Cefoxitin
- Imipenem.
- Chloramphenicol (brain abscess).

❖ Antimicrobials for bone infection:

- Agents against staph & gram negative organisms (see above).

- **Antimicrobials for bacterial endocarditis:**
  - Gentamycin plus penicillin (or vancomycin).
- **Antimicrobials for pharyngitis** (streptococci)[15]
  - Penicillins: penicillin V, amoxicillin, penicillin G (severe cases).
  - Cephalosporins: cefuroxime, cefaclor, ….
  - Macrolides: erythromycin, azithromycin, clarithromycin.
- **Antimicrobials for otitis media** (streptococci, H influenza)
  - Amoxicillin (high dose, plus clavulanic acid in case of lactamase-producing H influenza).
  - Cephalosporins: cefuroxime, cefaclor, ceftriaxone (resistant cases) …..
  - Macrolides (if allergic to B lactams).
- **Antimicrobials for sinusitis** (streptococci, H influenza, anerobes)
  - Same drugs as for otitis media.
  - Doxycycline (broad spectrum, good penetration into sinuses).
  - Clindamycin (for anerobes).
- **Antimicrobials for dental infections:**
  - Amoxicillin (empirical treatment)
  - **Metronidazole** → added to penicillins if no improvement in 72 hours (in mixed infections dominated with anerobes)
  - Erythromycin/Azithromycin (in patients allergic to penicillins).
  - Clindamycin (third choice).
- **Antimicrobials for bacterial meningitis**[16]**:**
  - Cephalosporins: cefotaxime- ceftriaxone, cefepime.
  - Penicillin G.
  - Rifampicin.
  - Chloramphenicol (brain abscess).

---

[15] Most cases are viral requiring no treatment. Streptococci may be involved.

[16] Gentamycin may also be used in meningitis.

❖ Antimicrobials for biliary tract infection[17]:

- Cefoperazone – ceftriaxone- cefazolin.
- Rifampicin -Doxycycline.
- Ampicillin or amoxicillin.

❖ Antimicrobials for brucellosis[18]:

- First choice: Doxycycline + Rifampicin or aminoglycosides.

❖ Antimicrobials for typhoid fever:

- Ciprofloxacin (adults).
- Ceftriaxone (children).
- Others: Co-trimoxazole - amoxicillin - chloramphenicol.

❖ Antimicrobials for urinary tract infections (E coli (mainly), staph):

- Fluoroquinolones - Cotrimoxazole.
- Amoxicillin+ clavulanic acid.
- Urinary antiseptics: nitrofurantoin & methenamine.

❖ Antimicrobials for gonorrhea:

- Penicillins.
- Ceftriaxone (single dose).
- Fluorinated quinolones (ofloxacin & levofloxacin).
- Spectinomycin (single dose).

❖ Antimicrobials in pregnancy:

- Penicillins – Cephalosprins - Erythromycin.

❖ Antimicrobials contraindicated in infants & children:

- **Tertacyclines** → teeth discolouration & bone deformity.
- **Chloramphenicol** → grey-baby syndrome.
- **Sulfonamides** → kernicterus in newly-born.
- **Quinolones** → arthropathy (not routinely used below 18 years).

---

[17] Gentamycin may also be used in biliary infections.

[18] Alternative drugs for brucellosis: chloramphenicol + aminoglycosides or co-trimoxazole.

DRUG THERAPY OF AMEBIASIS

- Amebiasis is an infection produced by ingestion of cysts (non-invasive form) of E. histolytica. This organism can cause:
  - A. **Bowel lumen amebiasis**: Asymptomatic (carriers or cyst passers), may become symptomatic if left untreated.
  - B. **Tissue amebiasis**: cysts develop into trophozoites which feed on intestinal bacteria or invade submucosa of large intestine, resulting in:
    1. Intestinal infection: mild to moderate (no dysentery) or severe (dysentery).
    2. Amebic granuloma (ameboma) in intestinal wall.
    3. Extra-intestinal amoebiasis: liver abscess, pulmonary amoebiasis…

Antiamebic Drugs

Antiamebic drugs are classified into:

A. **Luminal amebecides** → eradicate the cysts (source of infection).

B. **Tissue amebecides** → effective against the trophozoites in tissues.

A. Luminal amebecides

Diloxanide – Iodoqinol – Paromomycin

I- Diloxanide

- 1st choice luminal amebicide used for asymptomatic luminal infections & with tissue amebicides in tissue amebiasis to eradicate source of infection.

Kinetics

- 90% of diloxanide is absorbed & the unabsorbed 10% is the active amebicide.

Side effects

1. Flatulence – nausea - abdominal cramps.
2. Teratogenic: CI in pregnancy & children.

II- Paromomycin

- Aminoglycoside antibiotic. Not absorbed & remains in GIT lumen.
- Direct luminal amebicide alternative to diloxanide.
- Also acts indirectly by ↓ intestinal bacterial flora (nutrients for amebae).

Side effects: GIT upset, e.g. diarrhea.

III- Iodoqinol

- 90% of the oral dose is retained in intestine (poorly absorbed).
- Luminal amebicide (toxic drug; alternative to other luminal amebecides).
- Also used in giardiasis.

Adverse effects:

1. GIT upset: nausea, vomiting, diarrhea.
2. Neurotoxicity: subacute myelo-optic neuropathy (SMON).
3. Thyroid enlargement.

Tetracyclines: kill intestinal bacterial flora which are nutrients for amebae.

B. Tissue amebecides

Metronidazole – Tinidazole

Chloroquine - Emetine - Dehydroemetine

I- Metronidazole (Flagyl) nitroimidazole

Mechanism of action:

- It is a prodrug activated by reduction of its nitro group in anerobes & sensitive protozoa→ disruption of DNA structure & function → cell death.
- Highly effective tissue amebicide & partially effective luminal amoebicide affect trophozoites not cysts (due to ↓ luminal concentration as it is completely absorbed).

Uses of metronidazole:

1. **Anaerobic protozoal infections:**
   a. Amebiasis (all forms except asymptomatic cyst passers).
   b. Others: Giardiasis - Urogenital trichomoniasis.
2. **Anaerobic bacterial infections:**
   - Pseudomembranous colitis due to clostridium difficile.
   - Brain abscess, ulcerative gingivitis & dental infections- leg ulcers.

Adverse effects:

1. GIT: unpleasant metallic taste, glossitis, stomatitis,nausea & vomiting.
2. CNS (serious): dizziness - vertigo - ataxia - neuropathy - convulsions
3. Dark urine – dysuria.
4. Neutropenia.
5. Enzyme inhibitor: ↑ warfarin level.
6. Disulfiram- like reaction with alcohol.
7. Teratogenic (CI in pregnancy).

II- Tinidazole (Fasigyn):

- Similar to metronidazole but more effective, longer t ½ & less teratogenic.

III- Chloroquine

Mechanism: tissue amoebicide used mainly in hepatic amoebiasis.

Adverse effects

1. GIT: nausea, vomiting, dyspepsia & abdominal pain.
2. Skin: pruritis, rash & discoloration. (CI. in psoriasis).
3. Eye: retinal degeneration – corneal opacities.
4. C.V.S.: quinidine like action (hypotension & arrhythmias if given IV).
5. Hemolytic anemia: in G6PD-deficient subjects.

Uses:

- Anti-amebic- anti-malarial.
- Rheumatoid arthritis.

IV- **Dehydroemetine & emetine** (more toxic)

- Tissue amebicide used in cases of severe intestinal or extraintestinal amoebiasis if metronidazole cannot be used.

Adverse effects: limit its use

1. Cardiotoxic: arrhythmia - CHF (given in hospital → ECG monitoring)
2. Severe pain at site of injection.
3. Neuromuscular weakness & fatigue.

Treatment of specific forms of amebiasis

A. Asymptomatic lumen amebiasis (cyst carriers):

Luminal amebicide: should be used to eradicate cysts[1]

1. Diloxanide (1st choice).
2. Paromomycin.
3. Iodoquinol.

Alternatives

B. Tissue amebiasis

- A course of luminal amebicide is always given with tissue amebicides to eradicate the source of infection.

1. Intestinal infection[2]

1. Metronidazole or tinidazole (1st choice).
2. Tetracyclines [3] (alternative in moderate cases)

Plus Luminal Amebicide

2. Extra-intestinal infections[4] (liver abscess...)

1. Metronidazole or tinidazole (1st choice).
2. Metronidazole + chloroquine (liver abscess only); if above drugs fail [5].

Plus Luminal Amebicide

---

[1] As carriers may become symptomatic or a source of infection:.

[2] Dehydroemetine or emetine (alternatives in severe cases).

[3] Or erythromycin

[4] Dehydroemetine or emetine (alternatives if relapse occurs).

[5] Aspiration of abscess – chloroquine is given only in liver abscess.

DRUG THERAPY OF MALARIA

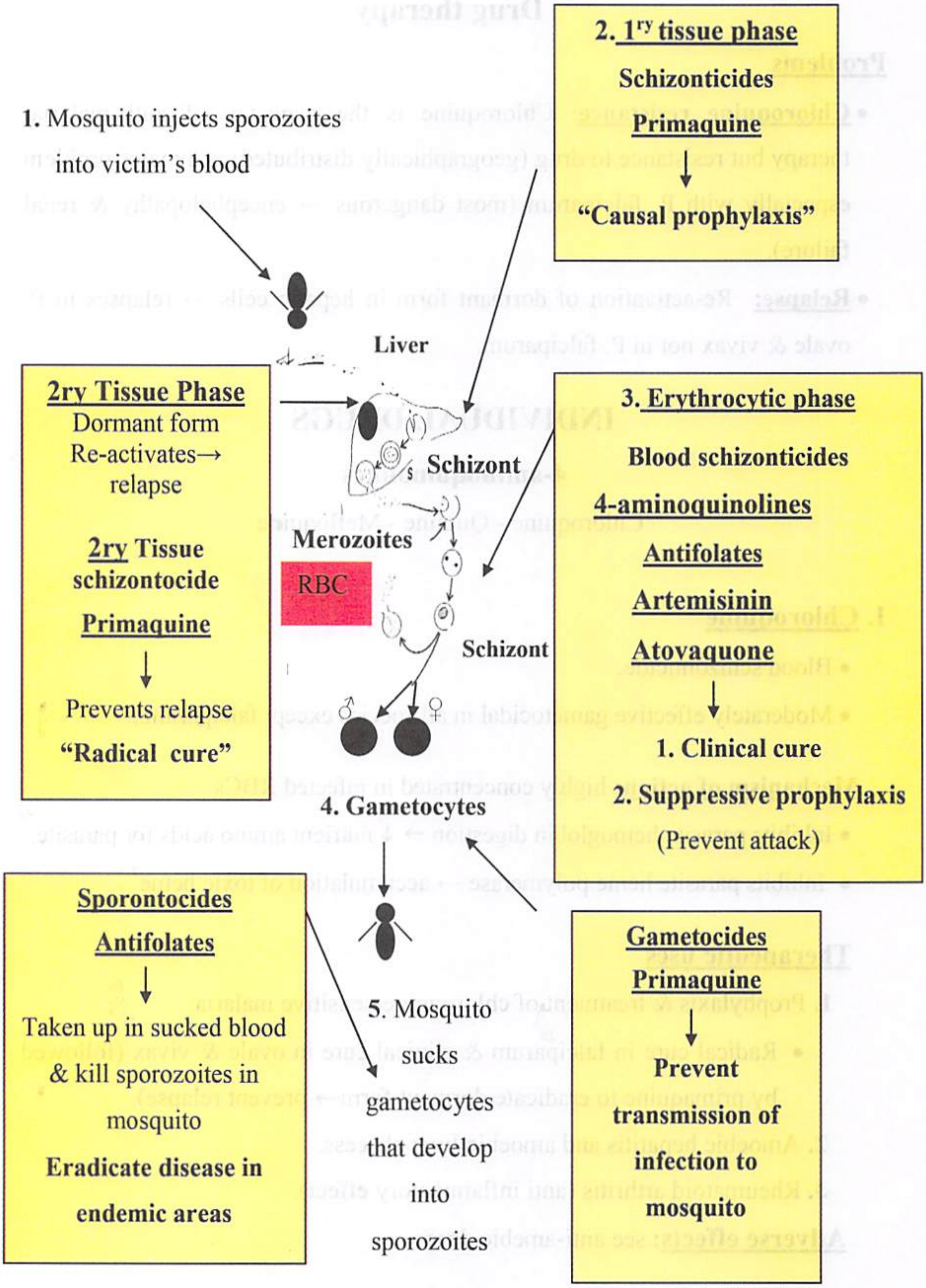
- Malaria is caused by 4 species of plasmodia (P): P. ovale, P. vivax, P. malaria & P. falciparum.

Life cycle of malaria

1. **Primary tissue phase** (pre-erythrocytic).
   - Infected mosquito[6] injects sporozoites into victim's blood which develop into shizonts in liver cells forming thousands of merozoites.
2. **Erythrocytic phase** (responsible for clinical picture)
   - Merozoites invade RBCs & develop into shizonts which form more merozoites.
   - Infected RBCs rupture releasing merozoites → clinical attack.
   - Merozoites re-enter fresh RBCs to repeat the erythrocytic phase.
3. **Secondary tissue phase** (exoerythrocytic)
   - Some parasites remain inactive in liver cells for months or years (dormant form). Re-activation of dormant forms in hepatic cells → relapse (in P ovale & P vivax only).
4. After several cycles parasites in RBCs may develop into male & female gametocytes that are infectious to mosquitoes.
5. Mosquitos pick up gametocytes that develop into sporozoites & are stored in salivary glands.
6. Life cycle is repeated when infected mosquitoes inject sporozoites into the blood of a new victim.

---

[6] Infection may result from blood contaminated needles.



1. Mosquito injects sporozoites into victim's blood

2. 1^{ry} tissue phase

Schizonticides

Primaquine

↓

"Causal prophylaxis"

2ry Tissue Phase

Dormant form Re-activates→ relapse

2ry Tissue schizontocide

Primaquine

↓

Prevents relapse

"Radical cure"

3. Erythrocytic phase

Blood schizonticides

4-aminoquinolines

Antifolates

Artemisinin

Atovaquone

↓

1. Clinical cure

2. Suppressive prophylaxis

(Prevent attack)

Sporontocides

Antifolates

↓

Taken up in sucked blood & kill sporozoites in mosquito

Eradicate disease in endemic areas

5. Mosquito sucks gametocytes that develop into sporozoites

Gametocides

Primaquine

↓

Prevent transmission of infection to mosquito

Life cycle of malaria & Site of Action of Antimalarial Drugs

Drug therapy

Problems

- **Chloroquine resistance**: Chloroquine is the mainstay of anti malarial therapy but resistance to drug (geographically distributed) is a major problem especially with P. falciparum (most dangerous → encephalopathy & renal failure).
- **Relapse:** Re-activation of dormant form in hepatic cells → relapses in P. ovale & vivax not in P. falciparum.

INDIVIDUAL DRUGS

4-aminoquinolines

Chloroquine - Quinine - Mefloquine

1. Chloroquine

- Blood schizonticide.
- Moderately effective gametocidal in all species except falciparum..

Mechanism of action: highly concentrated in infected RBCs

- Inhibits parasite hemoglobin digestion → ↓ nutrient amino acids for parasite.
- Inhibits parasite heme polymerase → accumulation of toxic heme[7].

Therapeutic uses

1. Prophylaxis & treatment of chloroquine-sensitive malaria:
   - Radical cure in falciparum & clinical cure in ovale & vivax (followed by primaquine to eradicate dormant form→ prevent relapse).
2. Amoebic hepatitis and amoebic liver abscess.
3. Rheumatoid arthritis (anti inflammatory effect).

Adverse effects: see anti-amebic drugs.

---

[7] Parasite splits HB into globin (nutrient amino acids for parazite) & heme. Heme polymerase polymerizes toxic free heme to hemozoin, rendering it harmless.

2. Quinine[8]

- Blood schizonticide with unknown mechanism of action.
- Treatment of chloroquine resistant falciparum but not in prophylaxis (too toxic).

Adverse effects:

1. Quinidine like action → hypotension & arrhythmias.
2. Eye → blurred vision and blindness.
3. Cinchonism: tinnitus - headache - dizziness and visual disturbances.
4. Black water fever & hemolysis[9].
5. Oxtytocic on uterus→ abortion

3. Mefloquine

Mechanism: Same as quinine but more effective- longer acting - less toxic.

Uses: Treatment & prophylaxis of chloroquine resistant *falciparum*.

Artemisinin & Derivatives

- Rapidly acting blood schizonticidal against all human malaria parasites.

Mechansm of action:

- Cleavage of the drug's endoperoxide bridge → free radicals.

Therapeutic uses

- Treatment of multidrug resistance P. falciparum.

Adverse effects:

- Nausea, vomiting, diarrhea.
- Prolonged QT interval.

Derivatives: Oral, rectal, IM; artesunate is also available IV

- Artemether (combined with lumifantrene [10]to decrease resistance).
- Artesunate (may be given with fansidar or combined with mefloquine).

---

[8] Weak antipyretic – weak muscle relaxant (used in muscle cramps).

[9] Allergic reaction to drug: marked hemolysis→ hemoglobinuria → black colour of urine

[10] Lumifantrene: related to halofantrine (blood schizonticide, active in all types. Cardiac problems limit its use to chloroquine resistant falciparum.

Atovaquone

- Active against tissue and erythrocytic schizonts.

Mechansm of action:

- Inhibits mitochondrial electron transport , ATP & pyrimidine biosynthesis.

Therapeutic uses: oral

- Prevention & treatment of choloroquine resistant falciparum (plus proguanil).

Adverse effects:

1. Headaches, nausea, vomiting, diarrhea.
2. Fever, rash.

8-aminoquinolines

Primaquine

- Tissue schizonticide & gametocide (unknown mechanism of action).

Therapeutic uses:

1. Radical cure of relapsing malaria (tissue schizonticide given after a blood schizonticide to eradicate dormant form).
2. Terminal prophylaxis of relapsing malaria (given after leaving the endemic area to ensure that dormant forms are eradicated)
3. Prevents transmission of disease to mosquito (gametocide).

Adverse effects:

1. Haemolytic anemia (in G6PDD)- methaemoglobinaemia .
2. Teratogenic.

N.B.: tetracycline & doxycycline are blood schizonticides (not used alone).

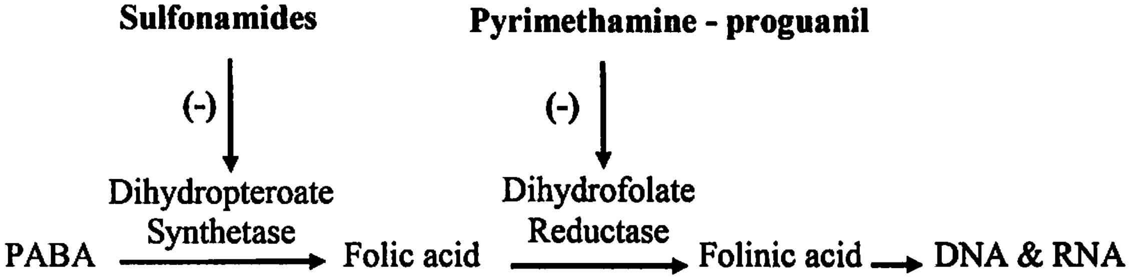
Antifolate Antimalarial drugs

Proguanil - Pyimethamine - Sulfadoxine.

- Blood schizonticides (mainly)– sporontocides.

Mechanism of action

- Inhibit folate pathway at 2 sequential steps→ inhibit DNA& RNA synthesis


Sulfonamides
Pyrimethamine - proguanil
(-)
(-)
Dihydropteroate Synthetase
Dihydrofolate Reductase
PABA
Folic acid
Folinic acid
DNA & RNA

Therapeutic uses:

1. Chloroquine resistant falciparum:
    - Atovaquone- proguanil.
    - Artesunate plus pyrimethamine + sulfadoxine (fansidar).
2. Toxoplasmosis: pyrimethamine + sulfadiazine.

Side effects:

1. GIT upset – hypersensitivity.
2. Megaloblastic anemia - haemolytic anemia (in G6PDD).

Treatment & Prevention of Malaria

	Treatment	**Prophylaxis**
Chloroquine Sensitive	**Chloroquine** + **Primaquine** (in vivax & ovale to prevent relapse)	
Chloroquine Resistant Falciparum	• Atovaquone- proguanil. • Artemether/ lumifantrene **OR** • Mefloquine • Quinine + doxycyline .	• Atovaquone- proguanil. • Mefloquine • Doxycyline

ANTIFUNGAL DRUGS

Fungal infections could be classified into:

A. Superficial fungal infections:

I. Dermatophytes:

Tinea: Capitis (scalp), Corporis (body), Inguinum (nails) & Pedis (foot)

II. Candida:

a. Cutaneous, vaginal, oropharyngeal and gastrointestinal candidiasis.

b. Mucocutaneous candidiasis in severely immunodefecient patients & can spread to deep tissues (disseminated).

B. Deep fungal infections:

Fungal pneumonia, gastroenteritis, endocarditis or meningitis.

Classification of Antifungal drugs

I- Drugs for systemic (deep) fungal infections:

1. Amphotercin-B.
2. Flucytosine.
3. Azoles: ketoconazole- fluconazole - itraconazole.
4. Caspofungin.

II. Drugs for superficial infections:

A. Drugs given systemically:

1. Griseofulvin.
2. Terbinafine.

} Dermatophytes

3. Azoles (ketoconazole, fluconazole, itraconazole): dermatophytes-candida.

B- Drugs given topically:

1.Nystatin (candida).

2.Terbinafine – naftifine (dermatophytes).

3.Azoles:ketoconazole – miconazole- clotrimazole[11](dermatophytes-candida).

4.Gentian violet (candida) - whitfield ointment (dermatophytes).

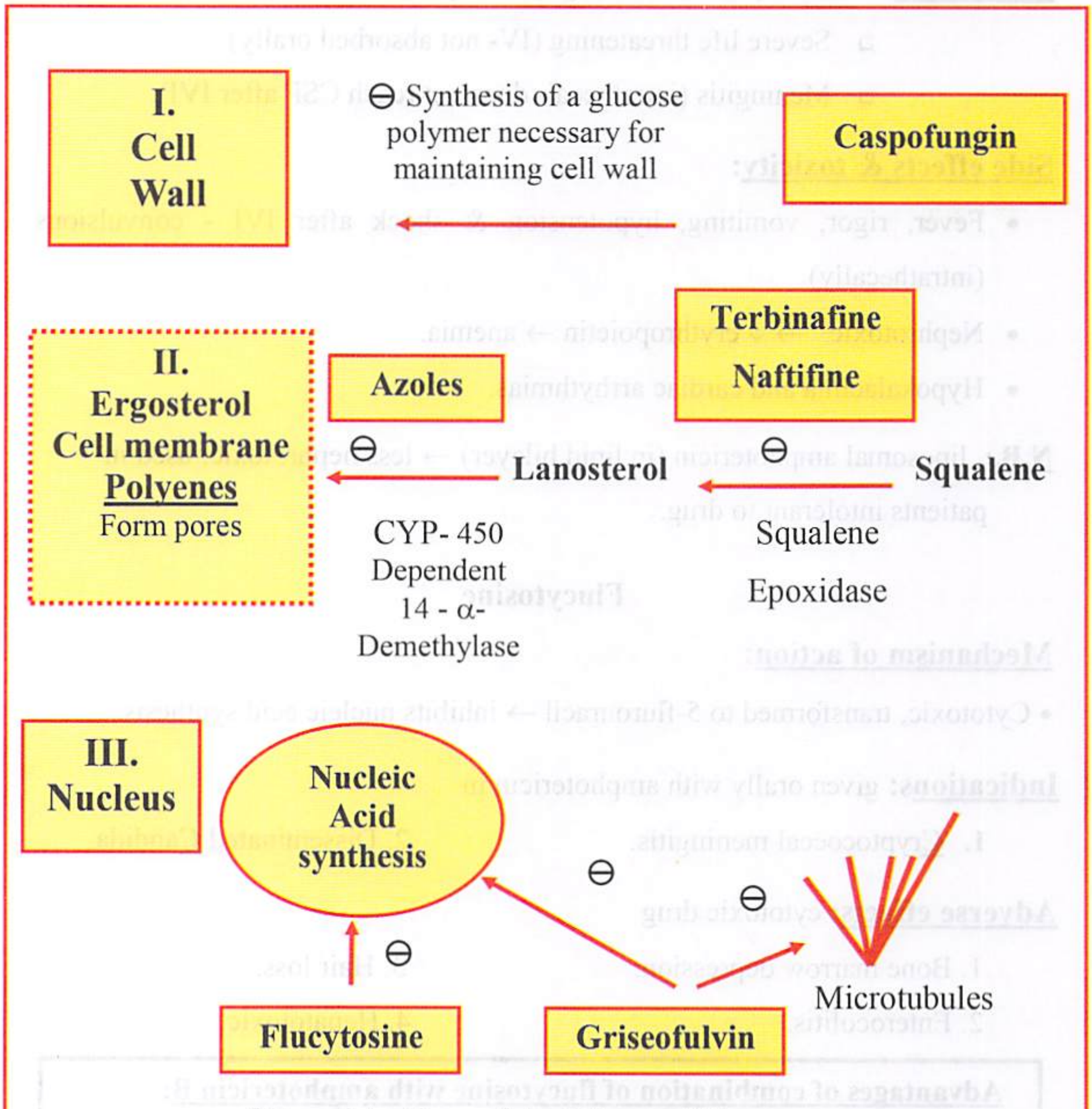
---

[11] Miconazole- clotrimazole are used only topically, too toxic for systemic use.

N.B.: Superficial fungal infections are treated first with topical agents.

Systemic therapy is used in:

1. Resistance to topical therapy.
2. Wide or inaccessible area.
3. Severe infections of hair - skin and nails.
4. Decrease immunity of patient


I.
Cell
Wall
⊖ Synthesis of a glucose polymer necessary for maintaining cell wall
Caspofungin
II.
Ergosterol
Cell membrane
Polyenes
Form pores
Azoles
⊖
Lanosterol
CYP- 450 Dependent 14 - α- Demethylase
Terbinafine
Naftifine
⊖
Squalene
Squalene Epoxidase
III.
Nucleus
Nucleic Acid synthesis
⊖
⊖
⊖
Microtubules
Flucytosine
Griseofulvin

Site of Action of Antifungal Drugs

N.B.: Polyenes: amphotericin & nystatin

INDIVIDUAL DRUGS

Amphotericin-B

Mechanism of action: fungicidal

- Binds to ergosterol of cell membrane → formation of artificial pores → leakage of important cell constituents → cell death.

Indications: Most important antifungal in deep infections especially:

- ◻ Severe life threatening (IV- not absorbed orally).
- ◻ Meningitis (intrathecal- does not reach CSF after IVI).

Side effects & toxicity:

- Fever, rigor, vomiting, hypotension & shock after IVI - convulsions (intrathecally)
- Nephrotoxic → ↓ erythropoietin → anemia.
- Hypokalaemia and cardiac arrhythmias.

N.B.: liposomal amphotericin (in lipid bilayer) → less nephrotoxic, used in patients intolerant to drug.

Flucytosine

Mechanism of action:

- Cytotoxic, transformed to 5-flurouracil → inhibits nucleic acid synthesis.

Indications: given orally with amphotericin in

1. Cryptococcal meningitis.
2. Disseminated Candida.

Adverse effects: cytotoxic drug

1. Bone marrow depression.
2. Enterocolitis.
3. Hair loss.
4. Hepatotoxic.

Advantages of combination of flucytosine with amphotericin B:

1. ↓ Resistance to flucytosine.
2. ↓ Amphotericin nephrotoxicity (lower doses of amphotericin are used).

AZOLES

Ketoconazole - fluconazole - Itraconazole

Mechanism of action: fungistatic

- Inhibition of ergosterol synthesis of cell membrane by inhibiting CYP450 dependent 14 - α- demethylase that converts lanosterol to ergosterol.

1. Ketoconazole

- **1st oral broad spectum antifungal for:**
  1. Deep fungal infections (mild - non meningeal) 2nd line to amphotericin
  2. Candidal infection.
  3. Dermatophytes resistant to griseofulvin & terbinafine (oral and topical).

Avoid combination with:

1. Antacids or H_2 blockers →↓ gastric acidity → ↓ ketoconazole absorption.
2. Amphotericin B : ketoconazole →↓ amphotericin effect by ↓ ergosterol (target for amphotericin).

Adverse effects

1. Nausea - vomiting – rash (common).
2. Hepatotoxic (serious).
3. Inhibition of human cytochrome P45o (serious)
   - **i) ↓ Steroid synthesis which depends on cytochrome P450:**
     - ↓ Corticosteroids → adrenal suppression (used in Cushing's disease).
     - ↓Testesterone → gynecomastia, impotence (used in cancer prostate).
     - ↓ Female sex hormones → menstrual irregularities, infertility.
   - **ii) ↓ Metabolism of drugs → drug interactions:**
     - ↑ Level of astemizole & terfenadine → arrhythmias.
     - ↑Level of oral anticoagulants, antiepileptics ......

N.B: Ketoconazole was discontinued in many countries as systemic antifungal. The less toxic & generally more effective triazole antifungal agents fluconazole and itraconazole are usually preferred.

2. Itraconazole and fluconazole (oral - IV)

- These drugs are azoles that are more specific to fungal cytochrome P450 than to human cytochrome P450 compared to ketoconazole.

Advantages of fluconazole and itraconazole over ketoconazole

1. Less toxic (less effect on human cytochrome P450): less hepatotoxic - less adrenal suppression - less drug interactions.
2. More effective.

Advantages of fluconazole over ketoconazole and itraconazole

1. Absorption is better and does not depend on acidity of stomach, therefore antacids or H_2 blockers could be taken safely with fluconazole.
2. Reaches CSF→ unlike ketoconazole it could be given in fungal meningitis.
3. Single dose → increases patient compliance.

Caspofungin

Mechanism:

- Inhibits synthesis of a glucose polymer that is necessary for maintaining structure of fungal cell wall→ loss of cell integrity→ lysis & death.

Uses (IV)

- Candidiasis & invasive aspergillosis refractory to amphotericin.

Adverse Effects (well tolerated): GIT upset - flushing.

Griseofulvin

Mechanism: Fungistatic

- Concentrated in newly formed keratin preventing its infection by:
  1. Interfering with microtubular function→ interfere with mitosis.
  2. Inhibiting nucleic acid synthesis.
- When infected keratin is shed it is replaced by uninfected one.

Indications

- Dermatophyte infections (orally; ↑ absorption by high fat diet).

Adverse effects (largely replaced by itraconazole & terbinafine)

1. Nausea-vomiting.
2. Headache - mental confusion
3. Hepatotoxic.
4. Enzyme inducer → ↓ warfarin level.

Terbinafine

Mechanism

- Inhibition of squalene epoxidase enzyme which is essential for ergosterol synthesis of cell membrane→ accumulation of toxic squaline.

Advantages over Azoles

1. Squalene epoxidase enzyme is not present in human.
2. No inhibition of cytochrome P450 (no serious adverse effect of azoles).

Indications:

- Systemic (oral) & topical for dermatophytes. More effective than griseofulvin.

Side effects (safe): GIT and taste disturbances.

Nystatin

Mechanism

- Binds to ergosterol of fungal cell membrane → formation of artificial pores→ damage of membrane → leakage of important cell constituents → cell death.

Indications: (too toxic for systemic use)

Used locally in:

1. Oropharyngeal and GI candida: oral (not absorbed).
2. Cutaneous candida: topical (nonirritant- rarely causes allergy).
3. Vaginal candida: It is given both topically and orally because quite often vaginal Candida is associated with gastrointestinal Candida which acts as a source of reinfection of vagina.

ANTIVIRAL DRUGS

- Viruses consist of nucleic acid (RNA or DNA) enclosed in a protein coat.

Types of viruses:

1. **DNA viruses:** herpes, hepatitis B, cytomegalovirus (CMV).....
2. **RNA viruses:** influenza, mumps, measles, HCV & poliomyelitis viruses...
3. **RNA Retrovirus :** HIV (contains reverse transcriptase enzyme)...

Steps of Virus replication & enzymes involved (targets for drug therapy)

1. **Adsorption- penetration & uncoating;** viruses have no metabolic machinery & have to enter host cell & use its metabolic processes to replicate.
2. **Early protein synthesis**: e.g., synthesis of viral RNA & DNA polymerases.
3. **Synthesis of RNA & DNA & coat proteins**: by RNA & DNA polymerases in RNA & DNA viruses respectively. In HIV, reverse transcriptase makes a DNA copy of viral RNA.
4. **Late structural protein synthesis** by viral protease→ viral protein processing → mature virion core.
5. **Assembly** of the formed nucleic acid & coat proteins into new viral particles.
6. **Release** of new viral particles from host cell; facilitated by neuroaminidase.

Immunoglobulins (γ-globulin)

- Pooled immunoglobulins (IgGs) containing antibodies against virus envelope → inhibition of viral adsorption & penetration.
- Used before[12] symptoms (viremia) → attenuates or prevent measles, infectious hepatitis, & poliomyelitis (passive immunization; offers 3weeks protection).

---

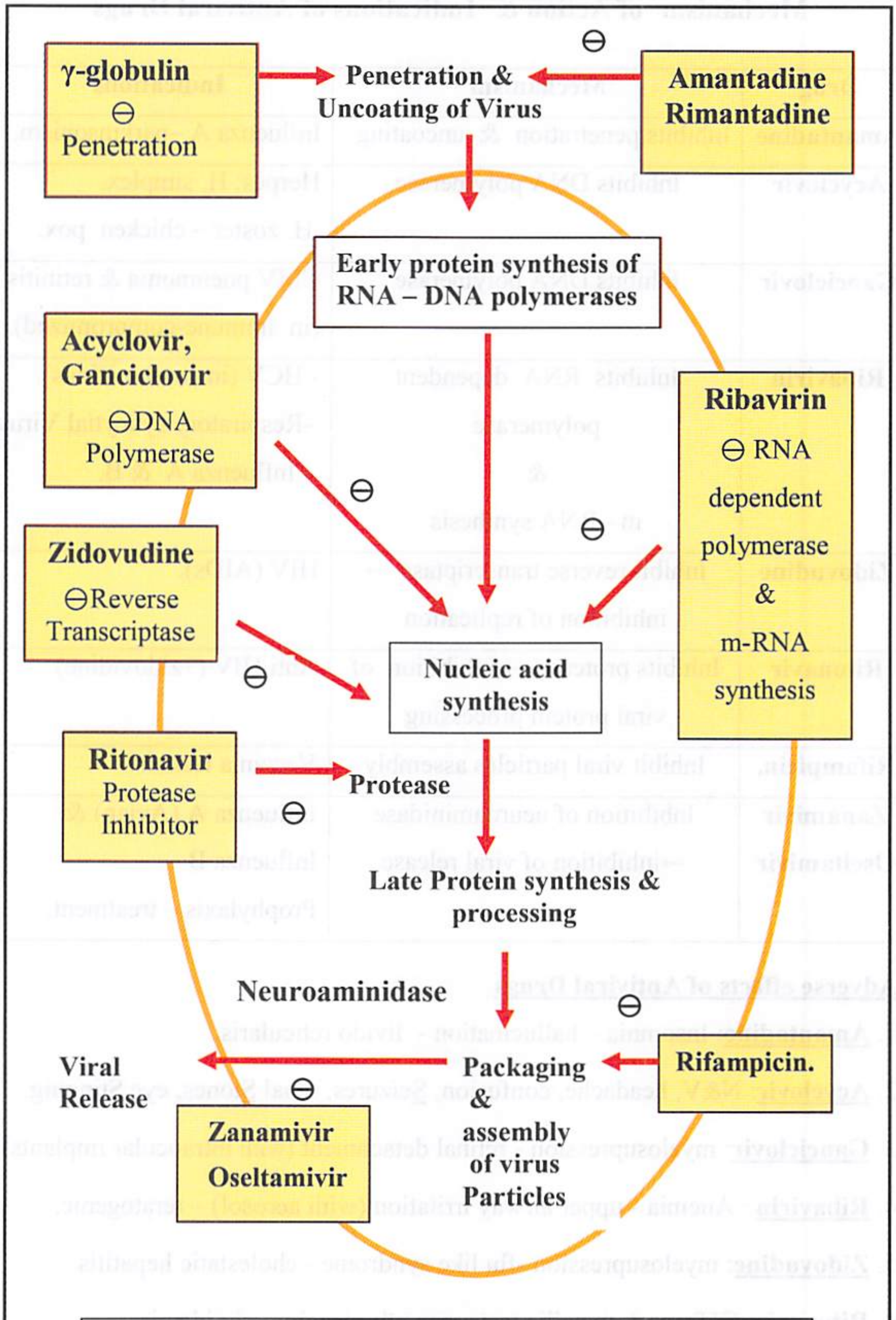
[12] Viral replication occurs before symptoms → antivirals must be used chemoprophylactically.

Mechanism of Action & Indications of Antiviral Drugs

Drug	Mechanism	Indications
Amantadine	Inhibits penetration & uncoating	Influenza A –parkinsonism.
Acyclovir	Inhibits DNA polymerase	Herpes: H. simplex. H. zoster – chicken pox.
Ganciclovir	Inhibits DNA polymerase	CMV pneumonia & retinitis (in immune-compromized).
Ribavirin	Inhibits RNA dependent polymerase & m - RNA synthesis	- HCV (in combinations). -Respiratory syncytial Virus - Influenza A & B.
Zidovudine	Inhibit reverse transcriptase → inhibition of replication	HIV (AIDs).
Ritonavir	Inhibits protease → inhibition of viral protein processing	Anti HIV (+zidovidine)
Rifampicin.	Inhibit viral particles assembly	Vaccinia lesions.
Zanamivir **Oseltamivir**	Inhibition of neuroaminidase →inhibition of viral release	Influenza A (Avian) & Influenza B Prophylaxis – treatment.

Adverse effects of Antiviral Drugs

1. **Amantadine**: Insomnia – hallucination - livido reticularis.
2. **Acyclovir**: N&V, headache, confusion, Seizures, renal Stones, eye Stinging.
3. **Ganciclovir**: myelosupression - retinal detachment (with intraocular implants).
4. **Ribavirin** : Anemia - upper airway irritation (with aerosol) – teratogenic.
5. **Zidovudine**: myelosupression -flu like syndrome - cholestatic hepatitis.
6. **Ritonavir**: GIT upset, metallic taste, parasthesias, hyperlipidemia.
7. **Zanamivir/ Oseltamivir**: N& V – nose & throat irritation (inhaled zanamivir).


γ-globulin
⊖
Penetration
Penetration & Uncoating of Virus
⊖
Amantadine
Rimantadine
Early protein synthesis of RNA – DNA polymerases
Acyclovir, Ganciclovir
⊖DNA Polymerase
⊖
Ribavirin
⊖ RNA dependent polymerase & m-RNA synthesis
⊖
Zidovudine
⊖Reverse Transcriptase
⊖
Nucleic acid synthesis
Ritonavir
Protease Inhibitor
Protease
⊖
Late Protein synthesis & processing
Neuroaminidase
⊖
Viral Release
Packaging & assembly of virus Particles
Rifampicin.
⊖
Zanamivir
Oseltamivir

Viral Replication in Host Cell & Mechanism of Action of Antiviral Drugs

Anti-viral agents for HCV

1. **Interferon (see below)**

2. **Ribavirin** (in combinations).
    - Inhibits RNA dependent polymerase & m - RNA synthesis.
    - **Side effects:** anemia - upper airway irritation (with aerosol) – teratogenic.

Newer agents:

- Anti HCV therapy progressed toward simpler IFN-free or IFN- & ribavirin-free regimens with shorter treatment durations & improved efficacy & safety.
- **Targets for newer anti HCV drugs include**
    - NS3, NS4A, NS4B, NS5A, and NS5B involved in synthesis of new viral RNA.
    - NS3- 4A (complex of NS3 & NS4A protein): a protease involved in viral protein synthesis.

1. **Sofosbuvir** (pro drug, nucleotide analog) [13]
    - Inhibitor of NS5**B** polymerase (RNA-dependent RNA polymerase).

    Side effects

    1. Fatigue, headache, irritability
    2. Nausea and rash.

    N.B.: Mainly renal elimination→ dose adjustment in renal impairment.

2. **Simiprevir**
    - Inhibitor of NS3- 4A protease.
    - **Side effect**: rash, pruritis.

3. **Ledipasvir**
    - Inhibitor of NS 5A (involved in replication & assembly of viral particle).
    - **Side effect**: Fatigue, headache.

---

[13] 400mg, once/day. Covers all genotypes (12 weeks for genotypes 1, 2 ,4; 24 weeks for type 3).

4. Others

- **Daclatasvir:** NS5A inhibitor
- **Ombitasvir**: NS5A inhibitor .
- **Dasabuvir** : NS5B polymerase inhibitor.
- **Paritaprevir**: NS3-4A protease inhibitor.

Combinations prescribed [14]

- Sofosbuvir/ Ledipasvir **(Harvoni).**
- Sofosbuvir **(Sovaldi)** plus ribavirin with or without peg-interferon.
- Sofosbuvir plus simprevir **(Olysio)**; sometimes given with ribavirin.
- Sofosbuvir plus daclatasvir **(Daklinza)**
- Ritonavir- paritaprevir, ombitasvir **(Technivie)** plus ribavirin.

N.B.:

- Paritaprevir is metabolised primarily by CYP3A4 thus it is given with a low dose of the CYP3A inhibitor ritonavir; this enables once daily administration and lowering the dose.
- Most side effects are due to ribavirin or interferon containing regimens . Fatigue, headache , influenza-like symptoms are reduced and neutropenia is absent in interferon-free treatment.

---

[14] Ritonavir- paritaprevir, ombitasvir tablet and dasabuvir **tablet (Viekera pack)**, sometimes given with ribavirin. Indicated in genotype 1 but is contraindicated in genotype 4.

Interferons

- Interferons (IFN) are endogenous proteins released by virally infected cells → ↓ susceptibility of neighboring cells to various DNA & RNA viruses.
- Purified interferons are prepared by recombinant DNA technology.

Types

- **IFN - α & IFN-β**: produced by B & T lymphocytes, macrophages & fibroblasts in response to viruses & cytokines → antiviral effect.
- **IFN γ:** produced by T lymphocytes in response to viruses, rickettsiae, protozoa → immunostimulant effect.
- **Pegylated IFN- α**[15]: ↑ efficacy & longer acting than IFN - α → SC once/wk.

Mechanism of action

- Bind to specific cell membrane receptors → inhibition of viral penetration, translation, transcription, protein processing, maturation & release.
- ↑ Phagocytic activity of macrophages.
- ↑ Proliferation of cytotoxic T cells.

Therapeutic uses of IFN - α

1. Hepatitis B & C.
2. Herpes: Disseminated infections in cancer patients.
3. HIV infection (AIDs).
4. Hairy cell leukemia (cytotoxic)

Adverse effects:

1. Flu like syndrome: fever, chills, myalgia & GIT upset.
2. CNS effects: dizziness - headache- confusion.
3. CVS effects: hypotension- arrhythmias.
4. Bone marrow depression.
5. Alopecia.

---

[15] Polyethylene glycol is attached to IFN- α→ large molecule

DRUG THERAPY OF HELMINTHIC INFECTIONS

Mechanism of Action of Anthelmintics

Paralysis

1. **Pyrantel Pamoate**:
   - Depolarizing NMB → spastic paralysis →worm expulsion.
2. **Levamisole.**
   - Depolarizing NMB & immunostimulant.
3. **Ivermectin**
   - ↑ GABA transmission (↑Cl^- influx)
4. **Praziquantel**
   - ↑ Permeability of worm cell membrane to Ca^{2+} → contraction followed by spastic paralysis, dislodgement & death.
5. **Metrifonate**
   - Organophosphorus choline esterase inhibitor → worm paralysis.
6. **Oxamniquine**
   - Unkown mechanism → worm paralysis→ hepatic shift & death.

Other Mechanisms

1. **Benzimidazoles**
   Inhibit microtubules synthesis →interfere with glucose uptake.
2. **Niclosamide**
   Inhibits glucose uptake & oxidative phosphorylation → scolex loosening & worm expulsion.
3. **Diethylcarbamazine**
   Alters surface structure of microfilariae displacing them from tissues → ↑ destruction by host defense mechanisms.

N.B.: In nematodes cholinergic receptors at NMJ are ganglionic nicotinic.

Indications of Anthelminthics

A. Drugs for Nematodes

I. Benzimidazoles

1. Mebendazole (ascaris, ancylostoma, enterobius, trichurius).

1. Enterobiasis: single 100-mg **chewed** tablet, repeated after 2 & 4 weeks.
    - All family treated at the same time + general hygienic measures
    - Local application of white precipitate ointment around the anal canal.
2. Other nematode infections: 100 mg twice daily for 3 successive days.
    - Fe is given in ancylostomiasis to correct the associated anemia.

2. Flubendazole: similar to mebendazole but also effective in strongyloides

3. Albendazole (broad spectrum for nematodes & cestodes)

1. **Nematode infection** (ascaris, ancylostoma, enterobius, trichurius):
    - Single oral dose 400 mg (repeat for 3 days for ascaris & in 2 wks for enterobius).
2. **Cestode infection** 1st choice in
    - a. Hydatid disease.
    - b. Neurocysticercosis: plus corticosteroids to ↓inflammatory reaction to dieing parasites.

4. Thiabendazole

1. Strongyloides (25 mg/kg twice/ day for 2 days).
2. Trichinosis (for 5 days).
3. Cutaneous larva migrans (for 2 days).

Chewed tablets given after meal

II. Pyrantel Pamoate

- Alternative to mebendazole in ancylostoma, ascaris & enterobius.

III. Levamisole

- Broad spectrum for nematodes.

IV. Antifilarial Drugs

1. Diethylcarbamazine

- Effective on blood microfilaria of Wuchereria bancrofti & loa loa.

2. Ivermectin: well tolerated

- 1ST choice for onchocerciasis - strongyloidiasis.
- Lice – scabies.

B. Antibilharzial Drugs

1. Praziquantel (broad-spectrum for trematodes & cestodes)

1. Schistosomiasis: 1st choice in all species.
20 mg/kg /4-6 hrs (3 doses).

2. Cestodes

- Taeniasis: 1st choice (single dose of 5-10 mg/kg).
- H. nana and D. latum infection (1st choice).
- Neurocysticercosis (2nd choice to albendazole) plus corticosteroids.
- Hydatid disease as an adjunct to albendazole pre- and post-surgery.

2. Oxamniquine (in mansoni) - metrifonate (in haematobium); rarely used.

C. Drugs for Cestodes: Praziquantel – niclosamide - albendazole

Niclosamide

- 2nd line to praziquantel for T. saginata & solium, D. latum & H. nana.
- Dose: 2 g (4 chewed tablets), single dose on empty stomach.

Precaution

In *T. solium* infection, a purgative is given to avoid cysticercosis; as damaged segments release ova which are not affected by drug.

Adverse effects (CI: GIT ulcers)

Drug	Adverse effect
1. Mebendazole/ flubendazole < 10 % absorbed	1. GIT pain & diarrhea. 2. Teratogenic (mebendazole).
2. Albendazole	1. GIT disturbances. 2. Headache – dizziness –insomnia. 3. Hepatotoxicity - pancytopenia & alopecia (in ttt of hydatid cyst).
3. Thiabendazole Complete absorption →more toxic	1. Anorexia, nausea & vomiting 2. Fatal skin reactions 3. CNS effects 4. Teratogenic (CI in pregnancy)
4. Pyrantel Pamoate	• Nausea, vomiting &diarrhea (mild).
5. Levamisole	• GI upset - allergy -CNS effects.
6. Diethylcarbamazine	1. GIT upsets (taken after meals). 2. Headache, arthralgia. 3. Allergic reactions to dying parasites: fever, rash, leukocytosis.
7. Niclosamide (Minimal absorption).	• Nausea & vomiting (rare)
8. Praziquantel (Well tolerated)	1. GIT disturbances. 2. Rash & pruritus & malaise. 3. Low-grade fever -eosinophilia. 4. Headache, dizziness, drowsiness 5.Teratogenic (CI in pregnancy)

CYTOTOXIC DRUGS

Cell Cycle Kinetics

- All cells undergoing division (cycling) pass through a group of phases of synthesis of RNA, DNA, mitosis and rest.

Classification of cytotoxic drugs according to phases of cell division

A- Cell cycle specific (CCS) → given to rapidly growing tumors:

- Antimetabolites - Vinca alkaloid - antibiotics as Bleomycin.

B- Cell cycle nonspecific (CCNS) → given to slowly growing tumors:

- Alkylating agents - antibiotics as dactinomycin, adriamycin.

I. Alkylating agents

Examples: cyclophosphamide, busulphan – nitrosoureas – cisplatin.

Mechanism:

- They are chemical substances containing highly reactive groups (alkyl).
- They transfer these active groups to various cellular constituents (mainly DNA, proteins and enzymes decreasing their synthesis &/ or functions.
- They are CCNS; effective against slowly growing tumours

II. Antimetabolites

Mechanism:

- They are structural analogues of naturally occurring metabolites competing with them for enzyme systems → ↓ DNA & RNA synthesis.
- They are cell cycle specific (CCS) effective in highly growing tumours

A. Methotrexate (folic acid antagonist)

- Inhibits dihydrofolate reductase → ↓ tetrahydrofolate synthesis → ↓ DNA & RNA synthesis.

B. 6- mercaptopurine (purine antagonist).

- Decreases purine synthesis → ↓ DNA and RNA synthesis.

III. Natural products

A. Plant alkaloids: (Vinblastine, Vincristine)

- They are mitotic spindle poisons → mitotic arrest.
- They are CCS used in rapidly growing tumors.

B. Antibiotics (adriamycin, methramycin and bleomycin)

- Bind to DNA → fragmentation of its strands → ↓ DNA synthesis

C. Enzymes (L- asparaginase)

- ↓ blood asparagine → deprives tumor cells of this amino acid which is essential for protein synthesis.

D. Interferons

IV. Hormones

They are used to suppress growth of hormone dependent tumours:

- Corticosteroids in leukemia and lymphomas
- Testesterone in Cancer breast.
- Estrogen in cancer prostate.
- Hormone receptors agonists & antagonists: (estrogen/tamoxifen), (testosterone/cyproterone, flutamide).
- Gonadotropin-releasing hormone agonists (leuprolide and goserelin) for prostate and breast tumors.

V. Radioactive isotopes

- Radioactive iodine (I^{131}), Phosphorus (P^{32}), Gold^{198} and Cobalt^{60}.

Mechanism:

- Emit β irradiations which cause destruction of the exposed tissues.

Uses:

1. Cancer thyroid.
2. Lymphomas.

Combination chemotherapy in cancer

Advantages:

1. Synergism: Each drug attacks tumour cells at different phases of growth cycle
2. Decrease incidence of resistance
3. Decrease incidence of adverse effects due to use of small optimal doses.

Adverse effects of cytotoxic drugs

A. General adverse effects:

1. Bone marrow depression: leucopenia, thrombocytopenia or pancytopenia.
2. Immunosuppression: liability to infections & delayed healing of wounds.
3. GIT disturbances: vomiting, diarrhea and GIT ulcers.
4. Hair loss.
5. Gonadal damage: sterility, amenorrhea and azospermia
6. Teratogenicity and mutagenicity.
7. Secondary malignancy
8. Hyperuricaemia (due to destruction of ↑number of tumor cells)

B. Specific adverse effects:

- **Cyclophosphamide:** haemorrhagic cystitis.
- **Busulphan:** interstitial pneumonitis and pulmonary fibrosis
- **Methotrexate:** mouth ulcer,hepatotoxic, pneumonitis, folate deficiency,
- **Vinca alkaloids:** peripheral & autonomic neuropathy.
- **Bleomycin:** pulmonary fibrosis – skin pigmentation.
- **Radiation:** skin reactions, necrosis, fibrosis, and fistula.

III. Immunomopharmacology

Intended Learning outcomes

By the end of this chapter, the student should be able to:

- Identify the major classes of immunosuppressant and immuno-stimulant drugs.
- Identify the mechanism of action , uses & adverse effects of different agents.
- Recognize the importance of the various uses of the newely introduced monoclonal antibodies (MAbs).
- Discuss choices of drugs used in rheumatoid arthritis according to the guidelines.
- Recognize the importance of methotrexate in rheumatoid arthritis.
- List the different therapeutic agents for autoimmune diseases.

Immunomopharmacology

The Immune System

- The immune system protects the body from invading pathogens & eliminates disease, while still capable of recognizing and toleratating "self" antigens.

Components of Immune System:

I. Innate (Natural):

- **Physical** → skin, mucus membrane (epithelial barrier)
- **Biochemical** → complement, lyzosyme, epithelial natural antibodies.
- **Cellular** → macrophages, neutrophils.

II. Adaptive (Acquired): 2nd line defense if innate immune response is inadequate

- **Humoral immunity**:→ B- lymphocytes →Ig antibodies → eliminate extracellular microbes & toxins.
- **Cell Mediated immunity** :→ T-lymphocytes (Kill bacteria, tumor cell& virus infected cell) →eliminate intracellular microbes.

N.B.: Antibodies mediate their functions by acting as opsonins to enhance phagocytosis and cellular cytotoxicity and by activating complement to elicit an inflammatory response →bacterial lysis.

Major Steps in Immune Responses

1- Antigen recognition.
2- IL-1 production.
3- IL-2 and other cytokine expression.
4- Lymphocyte proliferation & differentiation.

Abnormal Immune Responses

I. Hypersensitivity (see general pharmacology)

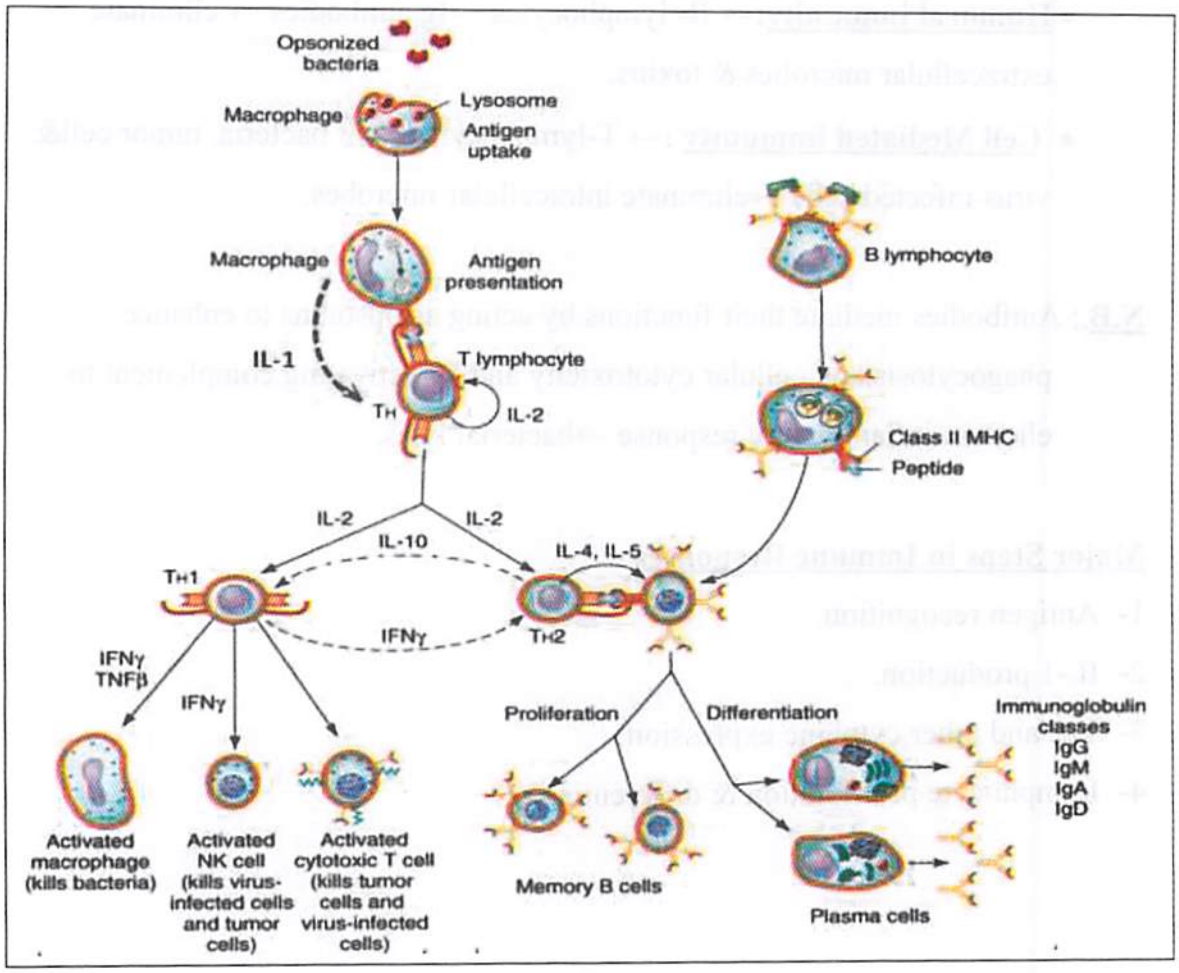
- **Immediate hypersensitivity**: usually Ig-mediated. (Type I,Type II, Type III)
- **Delayed hypersensitivity** (Type IV): cell-mediated

II. Autoimmunity:

- Activation of self-reactive T and B lymphocytes → cell-mediated or humoral immune responses against self antigens e.g Rheumatoid arthritis, systemic lupus(SLE), multiple sclerosis (MS), DM type I, etc…………

III. Immunodeficiency diseases:

- These are diseases resulting from inadequate function in the immune system → ↑ susceptibility to infections and prolonged duration & severity of disease.
- **Immunodeficiency diseases** may be either congenital (DiGeorge's syndrome) or secondary to bacterial or viral infections (AIDS) or drug treatment.


Opsonized bacteria
Macrophage
Lysosome
Antigen uptake
Macrophage
Antigen presentation
IL-1
T lymphocyte
TH
IL-2
B lymphocyte
Class II MHC
Peptide
IL-2
IL-2
IL-10
IL-4, IL-5
TH1
IFNγ
TH2
IFNγ
TNFβ
IFNγ
Proliferation
Differentiation
Immunoglobulin classes
IgG
IgM
IgA
IgD
Activated macrophage (kills bacteria)
Activated NK cell (kills virus-infected cells and tumor cells)
Activated cytotoxic T cell (kills tumor cells and virus-infected cells)
Memory B cells
Plasma cells

Drugs Acting on the Immune System

- Drugs affecting immune function are used for treatment of abnormal immune responses. They may be classified into:

  I. **Immunosuppressants**
  II. **Immunostimulants**

Immunosuppressants

1. Glucocorticoids (see Corticosteroids)

II. Calcineurins inhibitors: Cyclosporine- tacrolimus

A. Cyclosporine

Mechanism of action:

- Binds to an immunophyllin forming a complex that inhibits calcineurin (a protein necessary for activation of a T cell-specific transcription factor involved in synthesis of interleukins, e.g. IL-2) →↓cytokine production by T lymphocytes.

Adverse Effects[1]:

1. Nephrotoxicity (↑ with CYP450 inhibitors).
2. Hepatotoxicity.
3. Hypertension
4. Hyperglycemia

Uses

1. Organ transplantation & allogenic stem cell trasplantation[2].
2. Psoriasis
3. Rheumatoid arthritis.
4. Asthma

---

[1] Other side effects of cyclosporine: seizures , hirsutism, hypertrophy of gum, hperkalemia, cancers.

[2] Cyclosporine is used in treatment of host versus gaft disease following transplantation.

B. Tacrolimus

Mechanism of action & adverse Effects: similar to cyclosporine.

Uses

1. Organ transplantation.
2. Atopic dermatitis.
3. Psoriasis.

III. Proliferative signal inhibitors: Sirolimus

Mechanism of action:

- Binds to immunophyllin forming a complex that blocks mTOR[3] which is involved in cell proliferation & angiogenesis.

Adverse Effects

1. Bone marrow depression.
2. Hepatotoxic.
3. Hypertriglyceridemia.
4. Headache.

Uses

1. Solid organ transplantation & stem cell transplantation.
2. Dermatological disorders.
3. Sirolimus eluting stent: prevent restenosis by its antiproliferative effect.

IV. Mycophenolate Mofetil & mycophenolic acid:

Mechanism of action:

- Prodrug → mycophenolic acid →inhibits purine synthesis → selective reduction in T & B lymphocyte responses.

Adverse Effects:

1. Bone marrow suppression
2. Hepatitis.
3. Nausea, vomiting, diarrhea.

Uses

1. Hemopoietic stem cell transplantation.
2. Lupus nephritis.
3. Rheumatoid arthritis.
4. skin disorders

---

[3] mTOR: molecular target of rapamycin. It is a key component of a complex signalling pathway involved in cell growth, proliferation and angiogenesis.

V. Cytotoxic agents

1. **Methotrexate:** see rheumatoid arthritis

2. Azathioprine:

Mechanism of action:

- Metabolized to 6-MP → inhibits purine synthesis → inhibits DNA synthesis →cytotoxic effect on proliferating lymphocytes→inhibits cellular & humoral responses.

Adverse Effects:

1. Bone marrow suppression.
2. Hepatic dysfunction.
3. Nausea & vomiting.
4. Rash.

Uses[4]

1. Organ transplantation
2. Rheumatoid arthritis
3. SLE
4. Multiple sclerosis

3. Cyclophosphamide:

Mechanism of action:

- Alkylating cytotoxic agent: cross links DNA→inhibits cell replication → inhibits T cell & B cell function.

Adverse Effects:

1. Hemorrhagic cystitis.
2. Adverse effects of cytotoxic drugs: e.g., bone marrow depression,etc.

Uses

1. Rheumatoid arthritis.:for extra-articular manifestations as pericarditis.
2. SLE.
3. Multiple sclerosis.
4. Cytotoxic

---

[4] Other uses of azathioprine: chrons disease, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia.

VI. Monoclonal antibodies (MAbs) and immunoglobulin-based agents:

1. **Adalimumab -Etanercept & Infliximab**: TNF-α blockers
2. **Rituximab**:. Targets CD20 → depletion of β lymphocytes
3. **Abatacept**:. Binds CD80 & CD86 of antigen presenting cell.
4. **Anakinara**: Interleukin-1 receptor antagonist

see Rheumatoid Arthritis

5. **Basiliximab** (Anti-CD25): Anti-IL-2 Receptor
6. **Muromonab-(CD3)**: Binds to CD3→ internalization of T-cell receptor → prevents antigen recognition, signalling & proliferation.

used in Renal Transplantation

7. **Abciximab**: blocks gpIIbIIa platelet receptor→ prevents platelet aggregation and re-stenosis after coronary angioplasty
8. **Omalizumab**: Anti-IgE (used in treatment of bronchial asthma).
9. **Rh(D) immune globulin**: to Rh (-ve) mother after delivery.
10. **Thymoglobulin**: Anti-Thymocytes Polyclonal Globulin → removal of T-cell from the circulation →↓ cytokine response.

Therapeutics uses of Immunosuppressants

I. Organ transplantation & stem cell transplantation:

1. Corticosteroids
2. Azathioprine.
3. Mycophenolate Mofetil.
4. Cyclosporin
5. Tacrolimus.
6. Sirolimus.
7. Muromonab-CD3
8. Basiliximab.
9. Thymoglobulin

II. Cancer: e.g. Rituximab in B cell non-Hodgkin's lymphoma

III. Autoimmune & inflammatory diseases:

1. **Rheumatoid Arthritis, SLE, Multiple sclerosis (see below)**
2. **Psoriasis:** Corticosteroids, tacrolimus, cyclosporin plus Sirolimus.
3. **Bronchial asthma:** corticosteroids, omalizumab, sirolimus, cyclosporin.

IV. Angioplasty:

1. Sirolimus - eluted stent.
2. Abciximab: to prevent re-stenosis after angioplasty

II. Immunostimulants

Therapeutic uses: Immunodeficiency disorders, chronic infectious diseases& cancer.

Drug	Mechanism	Indications	Adverse effect
1. BCG vaccine[5]	• Activation of macrophages →more effective killer cells	• Intravesical "superficial bladder cancer"	• Hypersensitivity. • Shock, chills, fever. • Malaise. • immune complex
2.Thalidomide	• Immunomodulator: Favors TH2 over TH1. • Suppress TNF-α (antiinflammatory). • Antiangiogenesis: teratogenicity & anticancer	• Erythema nodosum leprosum (ENL). • Multiple Myeloma (MM).	• Teratogenicity, • Peripheral neuropathy. • Constipation. • Rash. • Hypothyroidism. • Thrombosis(DVT).
3. Levamisole (antihementhic)	• Restores depressed immune function of B-& T-lymphocytes, monocytes & macrophages.	• Given with 5-FU in class C colorectal cancer (only)	• Fatal Agranulocytosis Replaced by: 5-FU-leucovorin (more effective & less mortality)
4. Interleukin-2 (aldesleukin)	• T cell proliferation. • TH, NK, LAK cell activation	• Malignant Melanoma. • Renal cell carcinoma.	• Capillary leak syndrome[6]. • ↑ Disseminated infection
5. Interferons "IFNs"	See Antiviral Drugs.		

---

[5] Bacillus Calmette-Guerin-Vaccine (BCG):viable strain of *M.bovis* used for TB immunization .

[6] Capillary leak syndrome : loss of vascular tone → leak of plasma protein & fluid into extravascular space→ hypotension, ↓ organ perfusion, → death.

Drug Therapy of Rheumatoid Arthritis

- Rheumatoid arthritis is an autoimmune disease characterized by joint inflammation & subsequent tissue damage ➔ progressive deformities & joint damage.
- Immune complexes (IgM) activate complement & release cytokines (TNF-α & interleukin-1) which are chemotactic for neutrophils. These inflammatory cells release lysosomal enzymes ➔damage cartilage & erode bone.
- PGs released during the process➔ vasodilation & pain.
- **Drug Therapy**

A. Nonsteroidal anti-inflammatory drugs (NSAIDs).

B. Disease-Modifying antirheumatic drugs (DMARDs)

- Methotrexate (**drug of choice**).
- Hydroxychloroquine.
- Leflunomide.
- Sulphasalazine –penicillamine.
- Cyclosporine - -cyclophosphamide (see immunosuppressants)
- Azathioprine– gold (less commonly used due to ↑ toxicity & ↓ efficacy).
- **Biological agents** (monoclonal antibodies):
  1. TNF-α Inhibitors: adalimumab- etanercept – infliximab.
  2. Interleukin-1 inhibitors: anakinra.
  3. Anti CD 20 : rituximab.
  4. T- cell co-stimulation modulator: Abatacept.

C. Corticosteroids: e.g., Prednisolone.....

Guidelines for drug therapy of rheumatoid arthritis

1. Goal of therapy is to relieve pain, inflammation, swelling, stiffness and joint destruction thus avoiding joint replacement surgery.

2. Start therapy with NSAIDs: analgesic anti-inflammatory; reduce pain and swelling but do not prevent progression of disease & joint damage.
3. DMARDs therapy is started early once diagnosis is made to suppress the immune system →delay disease progress →prevent joint damage.
4. The onset of DMARDs therapeutic effects is delayed therefore NSAIDs or corticosteroids are given concurrently to relieve pain & inflammation until therapeutic effect of DMARDs is achieved.
5. Combinations of DMARDs are used as they lose effectiveness over time.
6. Corticosteroids are too toxic for chronic use and should be reserved for temporary control of severe exacerbation of inflammatory joint condition or for patients intolerant to DMARDs.
7. Monitor hepatic, renal & bone marrow function regularly to avoid drug toxicity.

Disease-Modifying Antirheumatic Drugs
(DMARDs)

1. Methotrexate

Mechanism of action:

- **Main effect** Inhibits aminoimidazole carboxamide ribonucleotide (AICAR) transformylase & thymidalate synthetase → 2^{ry} effects on polymorphonuclear chemotaxis.
- **Folic acid antagonist**: competitively inhibits dihydrofolate reductase→ ↓purine synthesis → ↓DNA → affects lymphocyte & macrophage function.
- **Direct effect**: ↓ cytokines -↓ inflammatory cell proliferation &↑ apoptosis .

Adverse Effects (best tolerated DMARDs)

- Nausea -mucosal ulcers (most common,↓ by folic acid).
- Bone marrow suppression (Regular blood count).
- Hepatotoxicity (Regular liver function tests).

- Pneumonitis (Regular chest radiology).
- **Drug interaction**: trimethoprim & sulfonamides:→↑antifolate effect on bone marrow (add folinic acid).

CI.: pregnancy- renal & liver disease

Uses: (Immunosuppressant, anti-inflammatory & cytotoxic[7])

1. Rheumatoid arthritis (of choice, most effective).
2. Psoriasis -SLE- Crohn's disease.
3. Leukemias , lymphomas, solid tumors.

2. Hydroxychloroquine

Mechanism of action: accumulates in lymphocytes, macrophages, polymorphs & fibroblasts→ inhibit phagocytosis (unknown mechanisms).

Proposed mechanisms:

- Inhibit T lymphocyte response to mitogens.
- Decrease leucocyte chemotaxis.
- Stabilize lysosomal enzymes.

Adverse Effects

1. GIT: nausea, vomiting, dyspepsia & abdominal pain.
2. Skin: pruritis, rash & discoloration (CI. in psoriasis)
3. Eye: retinal degeneration – corneal opacities (ophthalmic monitoring/6 m).
4. C.V.S.: quinidine like action (hypotension & arrhythmias if given IV).
5. Hemolytic Anemia: in G6PD-deficient subjects.

Uses

1. Rheumatoid arthritis.
2. Systemic lupus.
3. Stem cell transplantation.
4. Malaria

---

[7] Doses for rheumatoid arthritis are lower than those for malignant tumors.

3. Leflunomide[8]:

Mechanism of action:

- Inhibits dihydro-orotate dehydrogenase (DHODH) necessary for pyrimidine synthesis → prevents T cell proliferation & production of auto-antibodies by B cells .

Adverse Effects:

1. Diarrhea
2. Hepatoxicity
3. Alopecia.
4. Teratogenic.

Uses: rheumatoid arthritis

4. Sulfasalazine

Mechanism of action & Uses:

It is split by colonic bacteria into:

- **Sulfapyridine:** antifolate → ↓ cytokines release (interlukins & TNF-α) by monocytes → **immunomodulator in rheumatoid arthritis**
- **5-amino salicylic acid**→ **anti-inflammatory in inflammatory bowel disease.**

Adverse Effects

1. GIT upset. 2. Neutropenia. 3. Allergy to sulfonamides.

5. Penicillamine

Mechanism of action:

- ↓Immune response & IL-1generation.
- Prevents maturation of new collagen

Adverse Effects:

1. Skin rash.
2. Stomatitis, taste disturbance.
3. Proteinuria.
4. Nausea & vomiting.
5. Thrombocytopenia.

---

[8] Leflunomide is converted to its active metabolite in intestine & plasma & is as effective as methotrexate.

6. **Gold compounds** (auranofin, sodium aurothiomalate)

Mechanism of action: (unclear)

- Auranofin inhibits induction of IL- 1 and TNF-α.

Adverse Effects: (less with auranofin)

1. Skin rash & mouth ulcers.
2. Flu like symptoms.
3. Proteinuria.
4. Blood dyscrasias.

7. **Cyclosporine - -cyclophosphamide & azathioprine:** see immunosuppressants

8. **Biological agents (Monoclonal antibodies; MAbs)**

1. Adalimumab -Etanercept & Infliximab

Mechanism of action:

- Monoclonal anti TNF-α antibodies → combine with soluble TNF-α, preventing its interaction with receptor→ inhibit T cells & macrophages.

Adverse Effects: (more with infliximab)

1. Immunosuppression; respiratory infections (reactivation of TB).
2. Infusion reaction (infliximab)

2. Anakinara

Mechanism of action: (less effective than TNF-α inhibitors)

- Interleukin-1 receptor antagonist → prevents IL1 binding and suppresses inflammatory process in synovium.

Adverse Effects: Immunosuppression; respiratory infections.

3. Rituximab:.

Mechanism of action:

- Monoclonal antibody →targets CD20 on β lymphocytes → depletion of β lymphocytes →↓ presentation of antigen to lymphocyte &↓ release of proinflammatory cytokines→↓ inflammation.

Adverse Effects:

1. **Infusion reaction**: urticaria , hypotension, fever, chills & subsequent hypersensitivity reaction[9].
2. Exacerbates CVS disease (rare).

4. Abatacept:.

Mechanism of action:

- Monoclonal antibody: selectively binds to CD80 & CD86 of antigen presenting cell, blocking its binding to CD28 of T cell, preventing T cell activation.

Adverse Effects:

- Increase risk of infections (specially upper respiratory).
- Infusion reaction, hypersensitivity and anaphylaxis (rare).

---

[9] Avoid infusion reaction with rituximab by pre-treatment with corticosteroid or antihistamine.

Management of SLE

- Hydroxychloroquine: mild cases
- Azathioprine- methotrexate - mycophenolate mofetil: potency > H.chloroquine.
- Corticosteroids: in flares & severe cases (nephritis).
- Cyclophosphamide severe cases (nephritis).
- Rituximab: moderate & severe cases in young and child bearing period.

Disease-Modifying Treatment of Multiple Sclerosis (MS)[10]

- Glucocorticoids.
- Interferons[11]: INF-β-1a and INF-β-1b (Avonex, Betaferon).
- Glatiramer acetate[12]: immunosuppressant, shifts T-cells from pro-inflammatory Th1 cells → regulatory Th2 cells that suppress inflammation.
- Natalizumab (Ig against integrin on leucocytes).
- Mitoxantrone, Fingolimod.
- Azathioprine-cyclosporine- cyclophosphamide- methotrexate-sulfasalazine.

---

[10] Inflammatory disease: demyelination & scarring of fatty myelin sheaths around axons in brain & spinal cord → neurological, cognitive, psychological...signs and symptoms.

[11] IFN-γ used for treatment of chronic granulomatous disease

[12] Copaxone

IV. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Drug Therapy of Gout

Intended Learning Outcomes (ILOs)

By the end of this chapter, the student should be able to:

- Recognize the advantages of NSAIDS over opioid analgesics.
- Explain why aspirin is used as an antiplatelet drug while other NSAIDS are not.
- List the indications of aspirin at different dose levels.
- Recall the adverse effects specific to aspirin & those common with other NSAIDs.
- Explain why NSAIDS are nephrotoxic specially in hypovolemic patients.
- Explain why aspirin increases bleeding tendencies.
- Compare between different members of NSAIDS regarding efficacy & side effects.
- Explain why indomethacin is reserved for serious joint diseases.
- Discuss the possible drug interactions of NSAIDs.
- Explain why COX 2 inhibitors are dangerous in patients with a history of transient ischemic attacks.
- Explain why paracetamol has weak anti-inflammatory effect.
- Explain why paracetamol is preferred to aspirin in patients with gout
- Discuss the advantages of paracetamol over aspirin.
- Explain why the dose of paracetamol should not exceed 4g/day.
- Recall the advantages & uses of intravenous paracetamol.
- Discuss the strategy for gout therapy.
- Describe the mechanism of action of antigout drugs.
- Recall the most common adverse effect of colchicine.
- Explain why allopurinol and uricosurics have to be combined with anti-inflammatory drugs in the first 2 months of treatment.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

& Drug Therapy of Gout

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group having anti-inflammatory, analgesic & antipyretic effects. They include:
  - I. **Prototype NSAID: acetylsalicylic acid** (aspirin).
  - II. **Non selective NSAIDs: (ibuprofen, naproxen, diclofenac, piroxicam, indomethacin).**
  - III. **Selective COX-2 Inhibitors: Celecoxib.**
- Paracetamol is an analgesic-antipyretic with weak anti-inflammatory action.

Cyclooxygenase Enzymes

- **COX-1:** Mainly constitutive (present normally in tissues regulating its physiologic functions), responsible for forming protective PGs in GIT & kidney.
- **COX-2:** Inducible in inflammation, constitutive in endothelium & kidney.
- **COX-3:** Newly discovered (its role is still under investigation)

Mechanism of Action of NSAIDs & Paracetamol

- **Acetylsalicylic acid,** *irreversibly* inhibits (acetylates) cyclooxygenase enzymes (COX-1, COX-2) → inhibits conversion of arachidonic acid to endoperoxides → inhibits PG & TXA_2 production.
- Other **NSAIDs** cause competitive *reversible* inhibition of COX enzymes.
- **Celecoxib** is a selective inhibitor of COX-2 enzyme.
- **Paracetamol:**. Inhibits PG synthesis mainly in CNS → analgesic & antipyretic effects (may act on COX-3). Weak anti-inflammatory effect (poorly inhibits COX enzyme in the presence of excess peroxides in inflamed tissue). Its action may involve interaction with the seretonergic and endogenous opioid systems.

I. ACETYLSALICYLIC ACID (Aspirin)

Pharmacological Actions & Therapeutic Uses

Low-Dose

Prophylactic

1. Antiplatelet[1] (⊖ TXA_2 synthesis).
   Main use[2]: prophylaxis for transient ischemic attacks, unstable angina, acute myocardial infarction (but 300 mg in acute attack).
2. ↓ Risk of colorectal cancer.

High-Dose(4-8 g/d)

Anti-inflammatory

↓ PGE_2 & PGI_2 → ↓ VD & edema of inflammation.

Uses

1. Rheumatic fever.
2. Rheumatoid arthritis & other inflammatory joint diseases (NSAIDs replaced aspirin).

Intermediate dose (325 mg tab) 1-2 tab/4 h

Analgesic

a) **Peripheral effect:** ↓ PGs (that are released during inflammation & sensitize nerve endings to kinins) → ↑ pain threshold.

b) **Central effect:** ↓ PGs → ⊖ pain transmission at subcortical sites.

Uses

1. Mild to moderate pain 2ry to inflammation , e.g. arthritis, dental pain (ineffective in severe visceral pain).
2. Headache, dysmenorrhea.
3. Postpartum pain, postoperative & cancer pain (added to opioids to ↓ their dose).

Antipyretic

↓ pyrogen-induced PGE_2 in fever[3] → resetting of hypothalamic thermostat to normal → ⊕ temperature-regulating mechanisms → VD & sweating → ↓ temperature (no effect on normal temperature).

Uses

- Antipyretic in fever (paracetamol preferred).

---

[1] There is no difference in efficacy between doses of 75 to 150 mg/day and 160 to 325 mg/day.

[2] Use of aspirin in 1^{ry} prevention of CV disease is weighed against risk of bleeding on individual basis.

[3] PGE_2 generated by inflammatory pyrogens → ↑ hypothalamic set point for temperature control in fever.

Pharmacokinetics

- Aspirin is given orally & is rapidly absorbed partly from stomach (largely nonionized in acidic medium) & mostly from upper small intestine.
- Bound to albumin → displaces warfarin potentiating its effect[3].
- Rapidly hydrolyzed into acetic acid & salicylate by tissue & blood esterases ($t_{½}$ 15 min), followed by conjugation (saturable) → follows dose dependent elimination ($t_{½}$ varies from 2 hrs in low doses up to 30 hrs in toxic doses).
- Alkalinization of urine ↑ its excretion (useful in toxicity).

Adverse Effects

A. **Effects Common to all NSAIDs** (particularly in the elderly)

1. **GIT** (most common; direct mucosal irritation & ↓protective PGs)
   Dyspepsia, nausea, vomiting, gastritis, ulceration with ↑ risk of bleeding.
   Reduced by co-administration of misoprostol or omeprazole.

2. **Nephrotoxicity**[4] (less frequent with aspirin)
   In renal insufficiency or in hypovolemic patients whose GFR depends on vasodilator PGs (e.g. heart failure or extensive diuretic therapy), ↓ vasodilator PGs by NSAIDs → ↓ renal blood flow resulting in:
   a. Salt & water retention (edema), ↑ BP.
   b. Hyperkalemia.
   c. Acute renal insufficiency

3. **Hypersensitivity reactions:** Skin rash, rhinitis, asthma especially in asthmatics & patients with nasal polyps (diverts arachidonate metabolism from cyclooxygenase to lipooxygenase pathway → ↑ chemotactic LTB_4 & spasmogenic LTs).

---

[3] Aspirin should not be added to anticoagulant therapy except in specific conditions e.g. recent acute coronary syndrome or stent placement.

[4] Analgesic nephropathy: irreversible chronic interstitial nephritis due to abuse of mixed analgesics.

4. ↑ **Bleeding tendency** (stop aspirin 1 week before surgery)
   - Antiplatelet effect.
   - Displacement of warfarin from plasma proteins potentiating its effect.
5. **C.V. events (except with low dose aspirin)**

   There is an increased risk of adverse cardiovascular events: (MI, stroke, HF, AF and cardiovascular death), naproxen seems to have the least risk.
6. **Hepatotoxicity: Idiosyncratic reaction**
   - Severity vary from asymptomatic elevations in liver tests to fulminant hepatic necrosis resulting in death
   - On an individual patient level, NSAIDs do not pose a very large risk of hepatotoxicity.

B. Effects Specific to Aspirin

1. **Hypoprothrombinemia:** ↑ bleeding risk (> 5 g/d competes with vit. K).
2. **Hyperuricemia** (low-dose aspirin in gout): competes with uric acid for excretion by organic acid secretory mechanism in renal tubules.
3. **Reye's syndrome:** encephalopathy and liver damage in patients with fever due to viral infection **(CI as antipyretic in viral infections)**.
4. **Chronic toxicity (salicylism)**: prolonged administration of large doses → dizziness, tinnitus, nausea & vomiting.
5. **Acute toxicity:** respiratory alkalosis (hyperpnea → washing out of CO_2) followed by respiratory acidosis (respiratory depression→ CO_2 retention) & metabolic acidosis (accumulation of acidic metabolites).

Advantages over opioid analgesics:

i. No dependence.

ii. No respiratory depression (in therapeutic doses)

II. Non selective NSAIDs

- Possess analgesic, antipyretic & anti-inflammatory effects (see aspirin).
- They are increasingly used in inflammatory joint diseases (osteoarthritis, rheumatoid arthritis & gouty arthritis), dysmenorrhea, renal colic & postoperative pain; in patients not responding to aspirin or intolerant to it.
- They are ineffective as antiplatelets since they inhibit COX reversibly → short antiplatelet effect. If taken with low dose aspirin they may attenuate its antiplatelet effect.

Adverse Effects: see before

Individual NSAIDs (differentiated by cost-effectiveness, efficacy & safety)

Ibuprofen

- First-choice in inflammatory joint disease: less effective than others but better tolerated (↓ incidence of side effects than other NSAIDs).
- May be used as antipyretic besides paracetamol, if needed.

Naproxen

- Related to ibuprofen: more potent, with moderate risk of adverse effects.
- Longer-acting (given twice daily) → ↑ patient compliance.
- Least risk of CV events.

Diclofenac

- Combines good efficacy (stronger than ibuprofen) with relatively low incidence of side effects (more than ibuprofen but less than indomethacin).
- A combination of diclofenac and misoprestol is available in some countries.

Piroxicam

- Strong anti-inflammatory with ↑ risk of GIT bleeding.
- Long-acting ($t_{½}$ 45 h), given once daily.

Indomethacin

- Strong anti-inflammatory.
- **Due to serious adverse effects its use is limited to**:
  1. Acute gouty arthritis.
  2. Rheumatoid arthritis, ankylosing spondylitis.
  3. Postoperative pain.
  4. Patent ductus arteriosus (inhibits PG synthesis closing the ductus).

Adverse Effects

1. Adverse effects common with other NSAIDs (see before).
2. CNS: dizziness, confusion, ataxia, severe headache (cerebral VD).
3. Aplastic anemia.

Drug interactions of NSAIDs

1. ↓ Effects of ACEIs (↓ BK – induced PG production).
2. ↓ Effects of diuretics.
3. Displace warfarin & oral hypoglycemics from plasma proteins.
4. ↑ Risk of gastric ulceration with glucocorticoids.

III. Selective COX-2 Inhibitors

Celecoxib

- Selective COX-2 inhibitors were developed to spare COX-1 enzyme, thus retaining their anti-inflammatory effects without the adverse effects resulting from inhibition of constitutive COX-1 in GIT and kidney.

Uses

1. Anti-inflammatory: used in chronic inflammatory musculoskeletal disorders (with less risk of gastric ulceration).
2. Acute pain or primary dysmenorrhea

Adverse Effects of COX-2 Inhibitors[5]

1. Nephrotoxicity (COX-2 is constitutive in kidney).
2. Stroke & infarction (COX-2 is responsible for endothelial PGI_2 synthesis).
3. Skin rash with celecoxib (structurally related to sulfonamides).

PARACETAMOL (Acetaminophen)

- It is an analgesic antipyretic with ***weak*** anti-inflammatory action.

It is preferred to aspirin in:

1. Patients allergic to aspirin.
2. Peptic ulcer (no GIT disturbances).
3. Gout (aspirin may cause hyperuricemia).
4. Fever due to viral infections (to avoid Reye's syndrome with aspirin).
5. Bleeding disorders (does not affect platelet function).

Dose

- **For Adults**: 1000 mg 3-4 times daily; orally. Maximum: 4 g daily.
- **For Children**: 10 to 15 mg/kg/4-6 h. Maximum 5 doses/d.

---

[5] Recently, COX-2 was also found to be constitutive in many tissues (kidney , endothelium...).

Kinetics

- Paracetamol is conjugated in the liver to inactive metabolites & only 5% is converted by mixed-function oxidases to a hepatotoxic metabolite (N-acetyl-p-benzoquinone) → deactivated by conjugation with glutathione.
- In toxic doses saturation of conjugating enzymes results in increased conversion of the drug to the toxic metabolite beyond the capacity of liver to conjugate it with glutathione → hepatotoxicity.

Adverse Effects & Toxicity

- Minimal adverse effects - well tolerated.
- Analgesic nephropathy with high doses for long periods.
- **Paracetamol hepatotoxicity** (in toxic doses [150 mg/kg[6]]: nausea and vomiting, followed in 24-48 h by liver damage)

  Treatment: Precursors for glutathione synthesis: acetylcysteine (orally or IV) or methionine (orally) can prevent liver damage if given early.

Intravenous paracetamol[7]

1. **Analgesic:** in mild to moderate postoperative pain → safe with opioid sparing effect (↓ opioid dose).
2. **Antipyretic:** in acute fever of infectious origin requiring IV therapy.

---

[6] Dose is much lower if given with enzyme inducers.

[7] Perfalgan

DRUG THERAPY OF GOUT

- Gout is a metabolic disease associated with increased body stores of uric acid due to increased production or reduced excretion of uric acid or both.
- Hyperuricemia is diagnosed if serum uric acid is > 7 mg/dl.
- Hyperuricemia may be asymptomatic or may result in precipitation of monosodium urate crystals in joints &kidney resulting in:
  - Acute attack of gouty arthritis.
  - Tophi in joints, kidney & other tissues.
  - Renal stones.

Etiology

Primary hyperuricemia & gout

- Inborn defect in purine metabolism; ↑ uric acid production or ↓ excretion.

Secondary hyperuricemia & gout

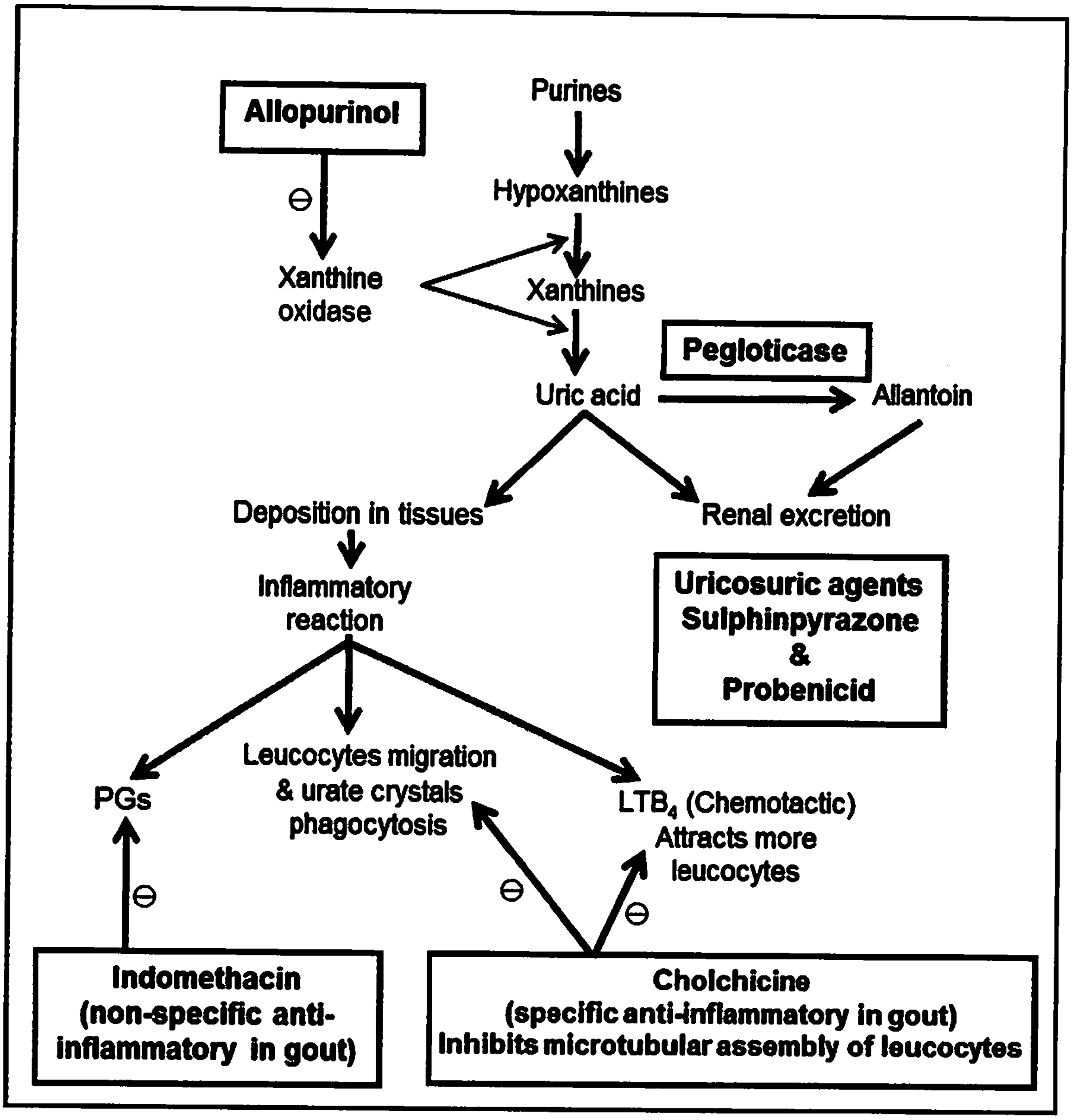
1. **Increased nucleic acid turnover:** tumors - hemolytic anemias…
2. **Reduced uric acid excretion:** chronic renal failure.
3. **Drug induced:**
   - **Aspirin:** small dose competes with uric acid for acid secretory system.
   - **Diuretics:** competes with uric acid for organic acid secretory system.
   - **Alcohol:** ↑ urate production (↑ nucleotides catabolism) - ↓ urate excretion.
   - **Cytotoxics:** ↑ uric acid production (↑ nucleic acid turnover).

Food increasing uric acid (avoided in gout)

- Meat (especially organ meat).
- Seafood.
- Beans.
- Alcohol.

Pathophysiology of gouty arthritis

- ↑ Uric acid → deposition of urate crystals in joints → pain & inflammation.
- The inflammatory reaction involves migration of leucocytes that phagocytose urate crystals → production of inflammatory mediators; PGs & LTB_4 (chemotactic for neutrophils) and oxygen metabolites → tissue damage.


Allopurinol
⊖
Purines
Hypoxanthines
Xanthine oxidase
Xanthines
Pegloticase
Uric acid
Allantoin
Deposition in tissues
Renal excretion
Inflammatory reaction
Uricosuric agents Sulphinpyrazone & Probenicid
Leucocytes migration & urate crystals phagocytosis
PGs
LTB4 (Chemotactic) Attracts more leucocytes
⊖
⊖
⊖
Indomethacin (non-specific anti-inflammatory in gout)
Cholchicine (specific anti-inflammatory in gout) Inhibits microtubular assembly of leucocytes

Mechanism of Action of Drugs Used in Gout

Treatment Strategies Include:

I. Decrease inflammation during acute attacks:

- NSAIDs, colchicine or glucocorticoids.

II. Increase uric acid excretion with uricosuric drugs:

- Probenecid - Sulfinpyrazone - Benzbromarone.

III. Inhibiting uric acid synthesis:

- Allopurinol (xanthine oxidase inhibitor).

IV. Conversion of uric acid to a water-soluble metabolite:

- Pegloticase

Management

A. Treatment of acute gout

- Anti-inflammatory drugs: NSAIDs or colchicine (if NSAIDs are contraindicated) or glucocorticoids (if both are contraindicated).

B. Long-term treatment

- Allopurinol.
- Probenecid – Sulfinpyrazone- Benzbromarone .
- Pegloticase.

A. Treatment of Acute Gout

I. NSAIDs (indomethacin-naproxen...)

- A potent oral NSAID, such as naproxen (500 mg twice daily) or indomethacin (50 mg three times daily).

II. Colchicine

Mechanism of Action

1. Selective inhibitor of microtubule assembly → ↓ leucocyte migration & phagocytosis.
2. Reduces production of leukotriene B_4 (chemotactic for neutrophils).

Indications

1. Acute gouty arthritis.
2. Mediterranean fever (unknown mechanism).

Dose in Acute Gouty Arthritis

- 1.2 mg then 0.6 mg one h later on 1st day, then 0.6 mg x 3/day till pain resolves.
- Dose is reduced to.0.6 mg once or twice/d for 2-3 days after complete resolution.

Toxicity (especially with high doses)

1. Nausea, vomiting, abdominal pain, and diarrhea.
2. With chronic administration: myopathy, neutropenia, aplastic anemia, and alopecia.

III. Glucocorticoids

- Choice of route depends upon number of inflamed joints, clinician experience with joint injection techniques & need for parenteral rather than oral therapy.

B. Long-Term Treatment

- Patients with hyperuricemia & repeated acute attacks of gouty arthritis or with chronic tophaceous gout (urate crystals deposited in tissues) should be treated with allopurinol as a first choice.
- Uricosurics are added in severe cases.
- Pegloticase may be used if other measures failed.

- Allopurinol, uricosurics or pegloticase may precipitate an acute attack (lowering of serum uric acid causes its withdrawal from tissues initiating an inflammatory reaction).
- To avoid precipitation of an acute attack, colchicine or an NSAID is combined with these drugs in the first 6 months of treatment.

I. Allopurinol

Mechanism

- Inhibits xanthine oxidase which converts hypoxanthine to xanthine & xanthine to uric acid → ↓ uric acid synthesis & urate pools.

Adverse Effects

1. GIT upset.
2. Precipitates acute attacks of gout.
3. Hypersensitivity[8].

II. Uricosuric Agents (Probenecid - Sulphinpyrazone, Benzbromarone)

Mechanism

- Directly inhibit URAT-1 (a urate–anion exchanger located at the apical brush border of the proximal nephron) and therefore reduce urate reabsorption

- In low doses, uricosurics may also compete with uric acid for renal tubular secretion & can even ↑ serum uric acid level.
- To avoid urate stones: increase fluid intake + alkalinize urine.

Adverse Effects

1. Acute attacks of gout.
2. GIT disturbances (peptic ulcer with sulphinpyrazone).
3. Hypersensitivity.

---

[8] **Febuxostat**, a xanthine oxidase inhibitor is an alternative for patients intolerant of allopurinol, patients with moderate chronic kidney disease, or who do not reach the target uric acid range with maximal doses of allopurinol.

III. Pegloticase

Mechanism

- It is a recombinant form of the enzyme urate oxidase or uricase.
- Urate oxidase converts uric acid to allantoin, a water-soluble nontoxic metabolite, which is excreted mainly by the kidneys.
- Pegloticase is used in patients with gout, who did not respond to xanthine oxidase inhibitors.
- It is administered as an IV infusion every 2 weeks.

Adverse Effects

1. Acute attacks of gout.
    - NSAID or colchicine is recommended for the first 6 months of therapy unless contraindicated or not tolerated.
2. Infusion reactions up to anaphylaxis.
    - Premedication with antihistamines & corticosteroids.
    - Close monitor of patients is required.

Contraindications

- Patients with G6PD deficiency.

V. CNS PHARMACOLOGY

Intended Learning Outcomes (ILOs)

By the end of this chapter, the student should be able to recognize the following ILOs:

Opioid Analgesics: the student should be able to

- Recognize the adverse effects of opioids as an extension of their widespread pharmacological actions.
- List the 2 most serious adverse effects of opioids.
- Explain why pethidine should not be used in chronic pain.
- Explain why fentanyl is preferred in anesthesia.
- Explain why remifentanyl induces less ventillatory depression than morphine.
- Explain why methadone and buprenorphine are used in detoxification of addicts.
- Identify the advantages of partial opioid agonists over pure agonists.
- Describe the impact of tramadol's dual opioid/ nonopioid analgesic mechanisms on its adverse effects & on management of its toxicity.
- Explain why naltrexone is used in management of chronic opioid toxicity (addiction) while naloxone is used in acute toxicity.

Anxiolytics and sedative-hypnotics: the student should be able to

- Describe the mechanisms of agents interacting with the GABA receptor complex.
- List the multiple actions of benzodiazepines & the uses of different members.
- Explain the advantages of selective hypnotics (e.g. zolpidem) and selective anxiolytics (e.g. buspirone) over benzodiazepines.
- Recognize that flumazenil antagonizes benzodiazepines & zolpidem but not buspirone or barbiturates.

Antidepressants

- Classify antidepressants according to their mechanism of action.
- List the adverse effects of tricyclic antidepressants and the advantages of the newer SSRIs and NSRIs over them.
- Discuss the disadvantages of nonselective MAOIs that restrict their use.
- Recognize the advantages of the reversible selective MAO-A inhibitors.

Antipsychotics: the student should be able to

- Describe the effects of blockade of dopamine receptors in different brain areas and the corresponding uses and adverse effects of antipsychotics.
- Discuss the differences in adverse effects between low & high potency agents.
- Discuss the advantages of the atypical agents over the older typical agents.

Antiepileptic drugs: the student should be able to

- Describe the mechanism of action of antiepileptic involving effects on brain transmitters and/or blockade of sodium or calcium channels.
- Discuss the choices of antiepileptics according to the type of epilepsy.
- Explain why barbiturates and benzodiazepines are not first choice agents.
- List the adverse effects of antiepileptics and the necessary precautions required during long term therapy of epilepsy.

- Discuss the lines of management of status epilepticus.
- Discuss the precautions required for antiepileptic therapy during pregnancy.

Antiparkinsonian drugs: the student should be able to

- Recognize that antiparkinsonian therapy aims to correct the imbalance involved in the pathophysiology of the disease by the use of anticholineric drugs or dopaminergic agents.
- Discuss the central and peripheral adverse effects of L-dopa .
- Explain how optimization of L-dopa therapy could be achieved by its combination with peripheral decarboxylase inhibitors (e.g. carbidopa), COMT inhibitors (e.g. entacapone), MAO-B inhibitors (e.g. selegilene) or dopamine agonists
- Recognize the use of apomorphine in emergency cases of sudden immobility.

Drug Abuse : the student should be able to

- List the major drugs that are commonly abused.
- Recognize that addictive drugs activate the mesolimbic dopaminergic reward pathway.
- Recognize that drug abuse occurs more with short-acting agents & withdrawal syndrome is more severe than that of longer-acting agents.
- Discuss management of withdrawal syndromes by detoxification & replacement of a short-acting agent by a longer-acting agent in the same group.
- Discuss other measures of management of withdrawal syndromes including aversion therapy (e.g. disulfiram for alcohol) or use of antagonists (e.g. naltrexone for opioids) or use of partial agonists (e.g. varenicline for nicotine).

General Anesthetics: the student should be able to

- List the commonly used intravenous anesthetics & describe their pharmacodynamic & pharmacokinetic characteristics.
- Discuss the major adverse effects of halothane & characteristics of newer inhalation agents.
- Recall the advantages of nitrous oxide compared to other inhalation agents.
- Recall 2 anesthetics with powerful analgesic effects.
- Describe the different anesthetic protocols e.g. conscious sedation, neuroleptanalgesia, neuroleptanesthesia, preanesthetic medication.

Local Anesthetics: the student should be able to

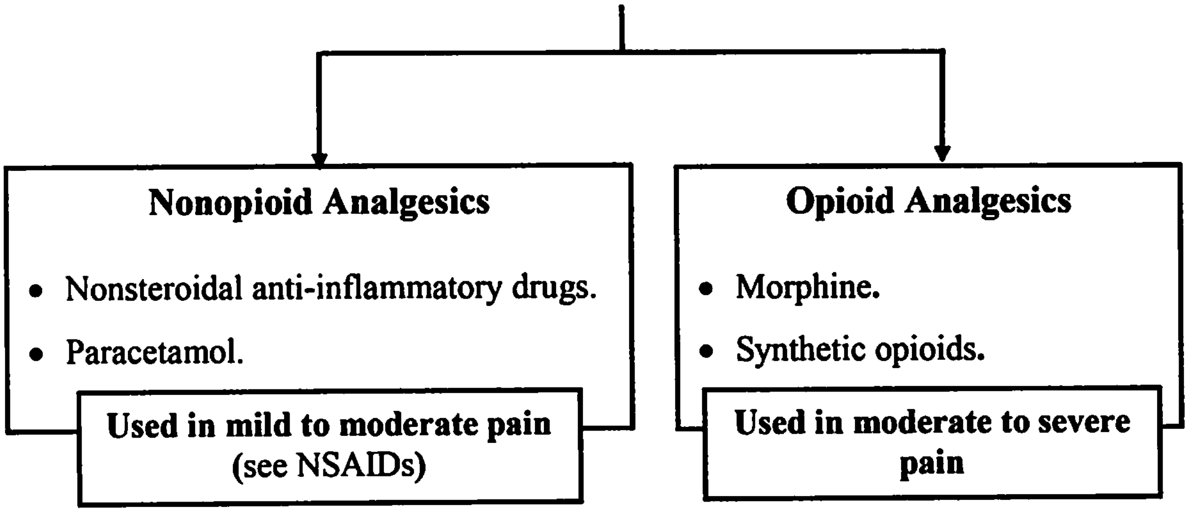
- Describe the mechanism of action of local anesthetics.
- List important members of the ester & amide groups & compare their characteristic features.
- Recall major adverse effects of local anesthetics.
- Discuss the importance of vasoconstrictors, tissue pH & drug pKa on activity of local anesthetics.

CENTRAL NERVOUS SYSTEM PHARMACOLOGY

ANALGESICS

- Analgesics are drugs that relieve pain due to multiple causes.

Classification of Analgesics



Nonopioid Analgesics

- Nonsteroidal anti-inflammatory drugs.
- Paracetamol.

Used in mild to moderate pain (see NSAIDs)

Opioid Analgesics

- Morphine.
- Synthetic opioids.

Used in moderate to severe pain

Opioid (Narcotic) Analgesics

- Opioids are drugs with morphine-like effects.

Sources

1. **Plant**: morphine - codeine (termed opiates; natural alkaloids; products of opium poppy).
2. **Synthetic**: fentanyl - methadone - heroin – pethidine….
3. **Endogenous**: endorphins - enkephalins - dynorphins (opiopeptides) released in the body, acting on opioid receptors, producing morphine-like effects.

Classification of Opioids

Opioid Analgesics

(see below)

Opioid Antitussives

(Less addictive than morphine)

- Codeine
- Dextromethorphan

(See Respiration)

Opioid Antidiarrheals

(Less addictive than morphine)

- Loperamide
- Diphenoxylate

(See GIT)

Mechanism of Action

Opioid receptors

- Mu (mediate most effects of opioids), kappa & delta, are Gi protein-coupled receptors present in the CNS and periphery (e.g. GIT).

Site of action of opioids

Opioids (directly or through release of opiopeptides) activate receptors in:

- Afferent pain-conducting fibers → **peripheral analgesia.**
- Spinal cord → **spinal analgesia.**
- Brain stem[1], thalamus & cerebral cortex → **supraspinal analgesia.**
- Limbic system → **euphoria & ↓ emotional response to pain** (patient may still feel the pain but the feeling is not unpleasant).

At the cellular level

Activation of receptors → neuronal inhibition through:

a. Inhibition of Ca^{2+} entry → ↓ release of excitatory neurotransmitters including substance P. (Presynaptic)

b. Stimulation of K^+ outflux → hyperpolarization of neuronal membrane. (Postsynaptic)

---

[1] Activation of opioid receptors in midbrain→ activation of inhibitory descending pathways to raphe nuclei in medulla→ to dorsal horn of spinal cord→↓ transmission in pain pathways ascending from spinal cord to thalamus, limbic & somatosensory cortex.

Actions, Uses, Adverse Effects & Contraindications (CI) of Morphine

Uses ←	Action	→ Adverse Effects & CI
1. Analgesic in: • Acute trauma. • Chronic visceral pain • Postoperative pain • Cancer pain • Myocardial infarction	**I. Main Effects** A. Analgesia ↓ Pain perception & emotional response to pain	• Masks pain *CI:* acute undiagnosed abdomen
	B. Sedation	• Sedation - Narcosis
2. In anesthesia • Preanaesthesia • CV surgery	C. Euphoria(or dysphoria)	• Drug dependence
3. Acute pulmonary edema in LVF following myocardial infarction: • ↓preload & after load • ↓Respiratory distress • ↓ Anxiety	**II. Inhibitory Effects** A. ⊖ VMC → venular & arterial VD	• Hypotension
	B. Respiratory center depression→↑ CO_2 → Cerebral VD & increased intracranial tension	• Respiratory depression & asphyxia neonatorum • ↑ Intracranial tension CI: head injury
4. Antitussive Replaced by Codeine Dextromethorphan (less addictive)	C. ⊖ Cough center	
	D. ⊖ Uterine tone → delayed labor	• Delayed labor
	III. Stimulatory Effects A. ⊕ Oculomotor nucleus → miosis	• Miosis
	B. ⊕ CTZ → vomiting	• Nausea - vomiting
5. Antidiarrheal Loperamide Diphenoxylate (less addictive, more widely used)	C. Urinary & GI Tracts ↑ tone of wall & sphincters (spasmogenic) but ⊖ peristalsis → stools stagnate & harden due to fluid absorption.	• Urine retention (also↑ ADH) (*CI:* enlarged prostate • Biliary colic(*CI*) • Constipation
	D. Histamine release	• Hypotension – itching - bronchospasm(*CI:* asthma)

Other effects: seizures & rigidity in ↑ doses. **CI**: age extremes - hypothyroidism - liver dysfunction (↓metabolism).Tolerance develops to all effects except constipation & miosis.

Classification of Opioid Analgesics

1. **Strong**	2. **Moderate**	3. **Weak**
A. **Pure Agonists** • Morphine • Fentanyl(& subgroup) • Methadone • Pethidine • Heroin B. **Partial agonists** • Buprenorphine	**Codeine** (Oral) • Analgesic plus paracetamol or aspirin in moderate pain. • Antitussive.	**Propoxyphene** (Oral) • Analgesic plus paracetamol or aspirin in mild to moderate pain.

N.B.: heroin & codeine are metabolized to morphine.

I. Pure Agonists

1. **Morphine** (see table).

Given IV - IM - SC - epidurally - orally (extensive 1st pass metabolism).

2. **Pethidine** [IM - Oral]

- Used in **ACUTE** moderate & severe pain e.g, trauma, postoperative pain, biliary colic or labor pain.

Pethidine differs from morphine in:

1. Less constipating (shorter acting).
2. Less respiratory depressant in neonates[2] & does not delay labor → preferred during labor (↓ risk of asphyxia neonatorum).
3. Atropine-like action: dry mouth, blurred vision,
4. ↑ Risk of convulsions (with high dose or in renal failure due to accumulation of toxic pethidine metabolite, norpethidine →**NOT used** for more than 48 hours.

---

[2] Morphine metabolism (conjugation) is deficient in newborns → longer depressant effect on respiration.

3. Methadone [Oral]

Uses

1. Treatment of opioid addicts (detoxification & maintenance):
    - Orally-active & long acting, thus, it is used to replace morphine or heroin in addicts. Gradual withdrawal of methadone is associated with less severe & smoother withdrawal symptoms.
2. Analgesic in severe chronic pain (efficacy equal to morphine).

4. Fentanyl

- More potent than morphine with rapid onset & shorter action (preferred in anesthesia).
- High anesthetic doses→ chest wall rigidity→↓ thoracic compliance → ↓ ventillation.

Uses (IV– epidural- spinal - transdermal patch – patient controlled infusion)

1. Analgesic in severe pain e.g. perioperative & cancer pain.
2. In anesthesia (for its analgesic & sedative effects):
    - Preanesthetic medication.
    - IV anesthetic in cardiovascular surgery (safer).
    - Conscious sedation - neuroleptanalgesia – neuroleptanesthesia.

Conscious Sedation & Neuroleptanalgesia

(Amnesia, sedation & analgesia without complete loss of consciousness)

Uses: minor procedures or for diagnostic purposes (e.g. endoscopy).

Conscious Sedation

- IV benzodiazepine (**e.g. midazolam**) - opioid analgesic (**e.g. fentanyl**).
- Easily reversed by flumazenil & naloxone (advantage).

Neuroleptanalgesia

- Neuroleptic (**e.g. droperidol**) plus opioid analgesic (**e.g. fentanyl**).
- Converted to **neuroleptanesthesia** by adding 65% nitrous oxide in O_2.

Fentanyl subgroup

- Sufentanil is more potent than fentanyl.
- Remifentanil (IV infusion): ultrashort acting as it is metabolized by blood & tissue esterases →less ventillatory depression.

5. Heroin

- Diacetylmorphine converted to morphine in CNS.
- Rapid onset (greater lipid solubility → crosses BBB more than morphine) & short duration → ↑ risk of abuse (not used clinically in most countries).

Oxycodone (oral & parentral)

- Opioid agonist inducing dose dependent analgesia.
- Used in acute and chronic pain.
- Combinations with aspirin or paracetamol are widely used.
- Drug of abuse (hillbilly heroin).

Tramadol (mixed opioid/nonopioid)

- Analgesic acting by inhibiting uptake of 5- HT and NA.
- Weak Mu agonist (only partially antagonized by naloxone).
- Less constipation, respiratory depression & addiction than morphine.
- ↑ Risk of convulsions.

Uses (oral, IM, IV)

- Analgesic in postoperative & chronic moderate pain & in neuropathic pain.

II. Partial Agonists

Buprenorphine (partial Mu receptor agonist)

Advantages over Pure Agonists

1. Less addiction (less euphoria → less craving).
2. Respiratory depression is not ↑ by ↑ dose (ceiling due to antagonist effect) but if it occurs, it is not easily reversed as it binds with ↑ affinity to receptors.

Uses (parentral, sublingual)

1. Analgesic in severe pain.
2. Alternative to methadone for treatment of opioid addicts (long-acting, slowly dissociates from receptors); given sublingually.

Drug Interactions of Opioids

1. Opioids + other CNS depressants (sedatives, alcohol, antidepressants & antipsychotics) → additive CNS depression.
2. Pethidine + MAOIs → serotonin syndrome (hyperpyrexia- convulsions)[3].
3. Partial agonist + pure agonist → withdrawal syndrome & ↓ analgesic effect.

Acute Morphine Toxicity

- Coma.
- Respiratory depression.
- Pin pointed pupil (diagnostic).

Treatment

- Support respiration.
- Naloxone (IV): opioid antagonist, repeated when necessary.

---

[3] Inhibition of pethidine metabolism by MAOIs → formation of the toxic metabolite, norpethidine, by another metabolic pathway.

Pure Opioid Antagonists

Naloxone

IV & short-acting

↓

Management of acute toxicity

1. **Acute opioid toxicity**
   Repeated as necessary to avoid relapse into coma since duration of action is shorter than opioids.
2. **Asphyxia neonatorum**
   Respiratory stimulant in opioid-induced respiratory depression in newborns.

Naltrexone

Oral & long-acting

↓

Maintenance therapy in addicts

1. **Opioid abuse**
   Blocks euphoria of opioids → loss of desire to take drug (prevents relapse).
2. **Alcohol abuse**
   ↓ Craving in chronic alcoholics (prevents relapse).

N.B.:

- Addicts should be closely monitored during reversal of acute opioid toxicity with naloxone to avoid precipitation of withdrawal symptoms.
- Naltrexone should be given to opioid addicts after full detoxification, otherwise it would precipitate a withdrawal syndrome

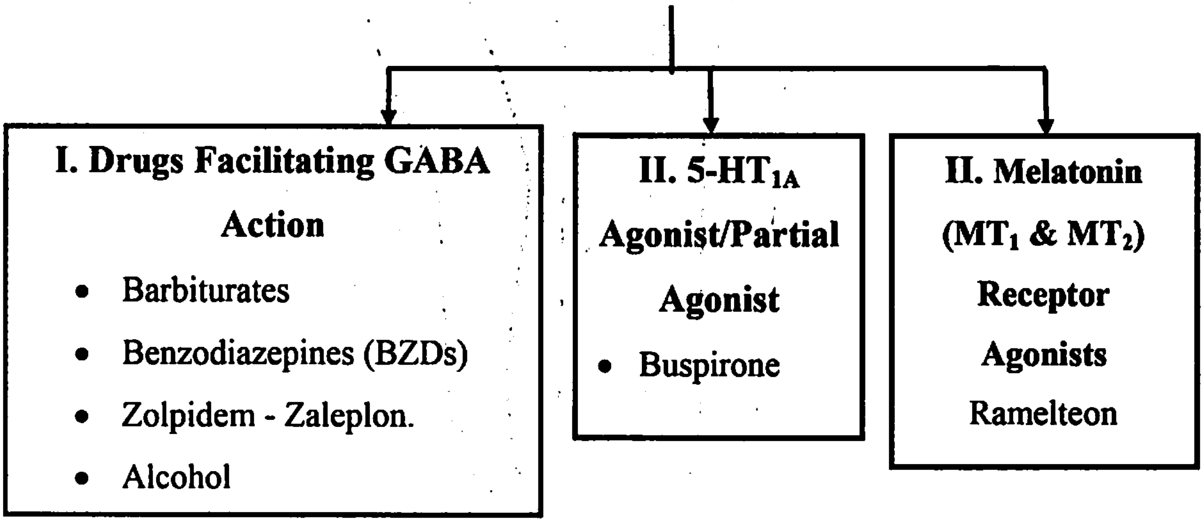
Alvimopan (oral)

- Antagonist on gastrointestinal Mu receptors (does not cross BBB).
- Blocks constipation, nausea & vomiting induced by opioids.
- Used in management of acute postoperative ileus.

ANXIOLYTICS AND SEDATIVE-HYPNOTICS

- Anxiolytics and sedative-hypnotics are drugs used mainly in treatment of anxiety and insomnia.

Classification According to Mechanism of Action



I. Drugs Facilitating GABA Action

- Barbiturates
- Benzodiazepines (BZDs)
- Zolpidem - Zaleplon.
- Alcohol

II. 5-HT$_{1A}$ Agonist/Partial Agonist

- Buspirone

II. Melatonin (MT$_1$ & MT$_2$) Receptor Agonists

Ramelteon

Other Drugs with anxiolytic or sedative-hypnotic Effects

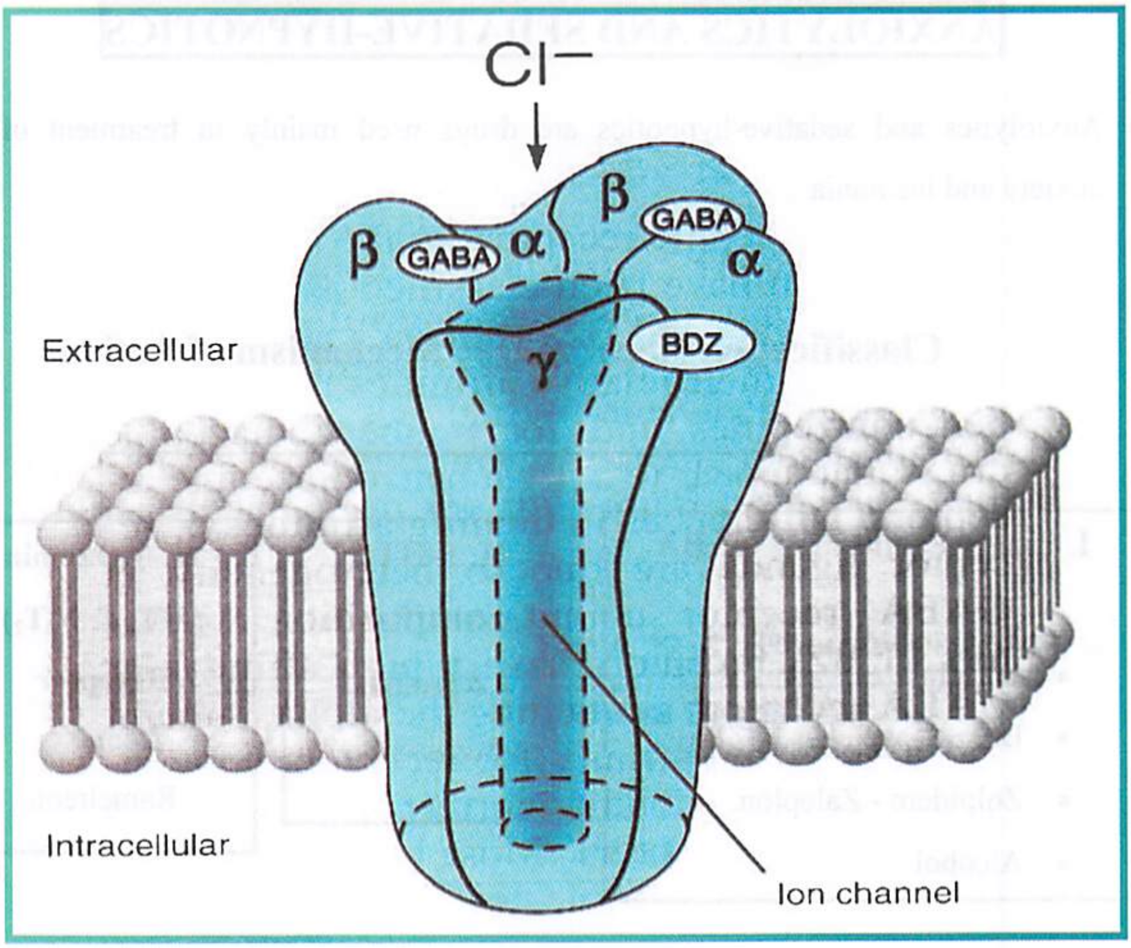
- Antidepressants.
- Antihistamines.
- β Blockers - clonidine (sympatholytics).

GABA Receptors

GABA$_A$ receptors: mediate postsynaptic neuronal inhibition.

GABA$_B$ receptors: mediate:

- **Presynaptic** neuronal inhibition by inhibiting Ca^{2+} influx → inhibition of release of the excitatory neurotransmitter glutamate.
- **Postsynaptic** neuronal inhibition by ↑ K^+ outflux → hyperpolarization.


Cl⁻
β
GABA
α
β
GABA
α
BDZ
γ
Extracellular
Intracellular
Ion channel

GABA$_A$ Receptor Cl- ion Channel Complex

- The GABA$_A$ receptor is a pentamer formed of 3 different types of subunits (two α, two β & one γ) surrounding a Cl$^-$ ion channel.
- The GABA binding site is at the interface between α and β subunits.
- BZD binding site is on γ subunit or an area on the α subunit regulated by γ subunit. located at the interface of the α subunit and the γ subunit on the GABAA receptor;
- Common BZ receptor subtypes in the CNS are designated as BZ1 or BZ2 depending on whether the binding site includes an α1 or α2 subunit, respectively.

Mechanism of action of drugs acting at GABA-A receptor Cl- ion channel complex

- **Binding of GABA** to its binding site between α and β subunits of GABA- A receptor opens a Cl^- channel with influx of Cl^- resulting in hyperpolarization and inhibition of neuronal firing.
- **Binding of BZDs to the BZD receptor** site of the GABA- A receptor complex →↑ affinity of GABA to bind to its receptors. This increases the **frequency** of opening of Cl^- channel facilitating the inhibitory effects of GABA.
- **Zolpidem binds to the BZD_1 receptor** subtype (involved in hypnosis) → facilitation of GABA inhibitory effect.
- **Barbiturates bind to a site near the Cl^- channel** distinct from the BZDs site. This results in increased **duration** of opening of Cl^- channel, facilitating the inhibitory effects of GABA.

Barbiturates

- More powerful CNS depressants than BZDs since in addition to enhancing GABA effect, barbiturates also have direct GABA-mimetic effects as well as inhibitory effects on glutamate receptors.
- Formerly used as sedative-hypnotics but largely **replaced** by BZDs due to:

1. **Narrow therapeutic index** (BZDs are safer)

   Barbiturates induce a dose-dependent CNS depression: sedation (at low doses), hypnosis (at higher doses) & anesthesia, coma, cardiovascular & respiratory depression → death (toxic doses).

2. **No specific antidote** is available for barbiturates whereas, flumazenil is a specific BZD antagonist.
3. **Drug dependence** is greater with barbiturates than with BZDs.
4. **Enzyme induction** occurs with barbiturates but not with BZDs → drug interactions.
5. **Acute porphyria**[4] may be precipitated by barbiturates in susceptible patients.

Members of Barbiturates

- **Long-acting**: phenobarbital (antiepileptic).
- **Short-acting**: pentobarbital, secobarbital (sedative-hypnotic).
- **Ultrashort-acting**: thiopental (IV anesthetic).

---

[4] Porphyrias are caused by deficiencies of specific enzymes of the heme biosynthetic pathway→ accumulations of toxic heme precursors; protoporphyrins) → skin or neurological complications. Barbiturates induce ALA synthetase enzyme responsible for synthesis of the porphyrins which accumulate since the enzymes responsible for their conversion into heme are defective.

Benzodiazepines (BZDs)

Diazepam – Clonazepam - Alprazolam
Lorazepam - Midazolam

- BZDs are the most widely used anxiolytics and sedative hypnotics.
- Prototype: diazepam

Pharmacological Actions & Uses of BZDs

I. Anxiolytic Euphoric

Potentiate GABA in limbic system

Uses

1- Generalized anxiety disorder & anxiety with other psychiatric illness
2- Panic Disorder

II. Sedative (low dose) Hypnotic (high dose)

Potentiate GABA in brainstem reticular formation

Uses

1. Insomnia :
   - Promote sleep onset
   - ↑ stage 2 of NREM
2. ↓ Night mares:
   ↓ REM sleep
3. ↓ Night terrors:
   ↓ Stage 3,4 of NREM sleep

III. Anesthetic

- Amnesia & sedation.
- Potentiate narcotics.

Uses

1. Conscious sedation.
2. Pre-anesthesia.
3. Balanced anesthesia , as adjuncts.

IV. Anticonvulsant (Antiepileptic)

Uses

Epilepsy
Status epilepticus

V. Skeletal Muscle Relaxant

(at spinal & supraspinal levels)

Uses

Muscle Spasticity in inflammation -trauma, cerebral palsy.

VI. Others

Cross tolerance with Alcohol
(Both Potentiate GABA)

Uses

Alcohol withdrawal (alcohol is replaced by a longer acting BZD → smoother withdrawal

N.B.

- Above actions are shared by all BZDs but **individual members differ in selectivity:**
    - **Alprazolam** is more selective in panic attacks.
    - **Diazepam** in muscle spasticity & alcohol withdrawal[5].
    - **Clonazepam** in long term treatment of epilepsy.
    - **Midazolam, lorazepam, & diazepam** in status epilepticus & in anesthesia.

Classification of BZDs according to duration of action[6]

1. Long-acting

- **Diazepam** [7](prototype):

  - Anxiolytic - anesthetic adjunct.

  - Anticonvulsant – skeletal muscle relaxant.

- **Clonazepam**:

  - Anxiolytic - anticonvulsant.

2. Intermediate →short acting

- **Alprazolam**[8]:

  - Anxiolytic - antidepressant.

- **Lorazepam**[9]:

  - Anxiolytic – hypnotic - anesthetic adjunct - anticonvulsant.

3. Ultrashort-acting (less than 6 hours)

- **Midazolam**:

  -Hypnotic - IV anesthetic.

---

[5] Chlordiazepoxide is a long acting BZD used in alcohol withdrawal.

[6] Temazepam: short acting BZD; anxiolytic - hypnotic.

[7] Duration of action of diazepam is 24- 48 hours.

[8] Duration of action of alprazolam is 24 hours

[9] Duration of action of of lorazepam is 14 hours. No active metabolite thus also used as a hypnotic.

Adverse Effects

1. Drowsiness – confusion - ↓ cognitive function[10] - hangover.
2. Amnesia (anterograde).
3. Ataxia & ↓ motor skills → difficulty in driving & ↑ risk of falls in elderly.
4. Abuse (tolerance & dependence; most serious, but less than barbiturates).
5. Additive CNS depression with alcohol and other CNS depressants.
6. Abnormal response: paradoxical excitement with short-acting agents.
7. Withdrawal of hypnotics →rebound insomnia & rebound ↑ in REM sleep[11].

Toxicity of Benzodiazepines

1. Prolonged sleep.
2. Respiratory & cardiovascular depression[12] (rare except if given rapidly IV or with other CNS depressants).

Antidote: Flumazenil

Flumazenil

- Competitive antagonist at BZDs receptor antagonizing BZDs & zolpidem.
- Short $t_{½}$; readministered after 1 hour to avoid recurrence of sedation.
- Effects on respiration are unreliable → monitor respiration.

Therapeutic Uses

1. BZDs toxicity.
2. Termination of BZDs effects in anesthesia.

Adverse Effects

1. Agitation.
2. Withdrawal syndrome or convulsions in BZDs dependent patients.

---

[10] Ability to understand, think , learn & judge .

[11] Shortening of REM sleep → anterograde amnesia, anxiety & irritability, followed by rebound increase with night mares on withdrawal. May occur in same night with short acting agents.

[12] May depress vital centers in infants (passes in milk) or in neonates if given in pre-delivery period.

Zolpidem

- Non-BZDs acting on BZD_1 receptor subtype involved in hypnosis.
- Ultra short-acting hypnotic[13] (an extended release preparation is available).
- Effects are antagonized by flumazenil.

Advantages of zolpidem over BZDs

1. Rapid onset.
2. Less cognitive impairment.
3. Less hangover[14].
4. Less tolerance & dependence with less rebound insomnia on stopping drug.
5. Less suppression of REM sleep[15].

Zaleplon:

- Similar to zolpidem in its hypnotic action with fewer residual effects on cognitive & psychomotor function due to its rapid elimination.

Ramelteon:

- Hypnotic; agonist at MT_1 & MT_2 melatonin[16] receptors in the brain.
- ↓ Latency to persistent sleep→ useful in patients with difficulty in falling asleep.
- Minimal abuse potential (not a controlled substance): no withdrawal symptoms or rebound insomnia.
- **Side effects**: dizziness, somnolence and fatigue.

---

[13] Duration of action of zolpidem is 4 hours.

[14] Drowsiness, headache, dysphoria, mental & motor depression occurring on day following drug intake.

[15] Does not shorten REM sleep as BZD thus no REM rebound ocurrs on stopping the drug.

[16] Melatonin hormone of the pineal gland maintains circadian rhythm of normal sleep -wake cycle.

Buspirone

- Agonist/partial agonist at 5-HT_{1A} (mechanism not fully understood).
- Differs from BZD: Selective anxiolytic (negligible sedation, no hypnotic, anticonvulsant or muscle relaxant effects).

Advantages

- No amnesia or ↓ cognitive function, or additive CNS depression with alcohol or other sedatives.
- No ataxia or reduction of psychomotor skills.
- No abuse (delayed onset & dysphoria), useful in patients liable to abuse.

Disadvantages

1. Delayed onset (requires one to two weeks to act).
2. Does not treat insomnia or panic attacks.

General Guidelines for Therapy with Sedative-Hypnotics

- Drug therapy is indicated only in severe acute anxiety or short term treatment of acute insomnia[17].
- Drug therapy should be started with a small oral dose for a limited period (4-6 weeks) to avoid drug abuse & dependence (major limitation to the use of BZDs).
- Termination of therapy should be gradual to avoid a withdrawal syndrome.
- The preferred agent for insomnia in patients with difficulty in falling asleep is an agent with rapid onset & short duration to avoid hangover; excessive sedation the following day, e.g. lorazepam, midazolam.
- Insomnic patients who complain of early morning awakenings & who require anxiolytic effect during the day should receive a longer acting BZD, e.g., diazepam.
- Chronic insomnia is usually associated with anxiety or depression thus should be treated with an antidepressant (e.g., mirtazapine).
- Acute anxiety is treated by BZDs or buspirone. Chronic anxiety is treated by antidepressants. BZDs are added to calm the patient until the antidepressant becomes effective.
- Longer-acting BZDs are preferred as anxiolytics since shorter-acting ones result in residual anxiety the following day.
- Panic Disorder requires highly potent drugs as alprazolam (its antidepressant effect is also useful). Buspirone is not useful.
- Most BZDs are metabolized in liver → dose adjustment is required in liver cirrhosis to avoid accumulation to toxic levels specially of long acting agents and those metabolized to active metabolites such as diazepam. Lorazepam has no active metabolites thus preferred in liver dysfunction.
- Dose of BZD should be reduced in elderly to avoid accumulation (reduced liver metabolism) & to reduce risks of falling due to drug induced confusion & ataxia.

---

[17] Drug therapy of anxiety should be accompanied by psychotherapy & relaxation techniques whereas that of insomnia should not be started except if alternative methods fail (bathing, exercise, milk....).

ANTIDEPRESSANTS

Depression is a mood disorder. It is classified into:

1. Unipolar depression

- **Major depressive Disorder (17%):** a genetically determined biochemical disorder manifested by inability to deal with normal stress of life.

2. Bipolar manic depressive disorder (4%)

- Episodes of depression alternating with episodes of mania.
- Manic attacks are characterized by decrease need of sleep, flights of ideas, grandiosity, euphoria, talkativeness, lack of judgment, psychomotor agitation & may be associated with psychotic symptoms (hallucinations, delusions).

Symptoms of Depression

- A major depressive episode is a period lasting at least two weeks, with five or more of the following symptoms: Sadness – inability to experience pleasure (anhedonia) - fatigue- loss of libido - disturbance in appetite & sleep (usually↓) - guilt – worthlessness - inability to concentrate or indecisiveness- psychomotor agitation or retardation- recurrent suicidal ideation.
- Psychotic symptoms (hallucinations & delusions) occur in severe depression.
- Symptoms cause significant impairment of social& occupational function.
- **Atypical Symptoms may occur** including overeating & ↑ sleep -anxiety - phobias – obsessions, hypochondriasis (multiple body complaints).

Monoamine Theory of Depression[18]

- Brain biogenic amines, norepinephrine (NE) & serotonin (5-HT) are neurotransmitters responsible for mood. ↓ Activity of these transmitters results in depression, whereas ↑ activity leads to mood elevation.

---

[18] Other theories : 1. ↓ Brain derived neurotrophic factor essential for survival & function of neurons. 2. Abnormalities in hypaothalamic pituitary adrenal axis & ↑ cortisol level. 3. Inflammatory theory............

Mechanism of Action of Antidepressants

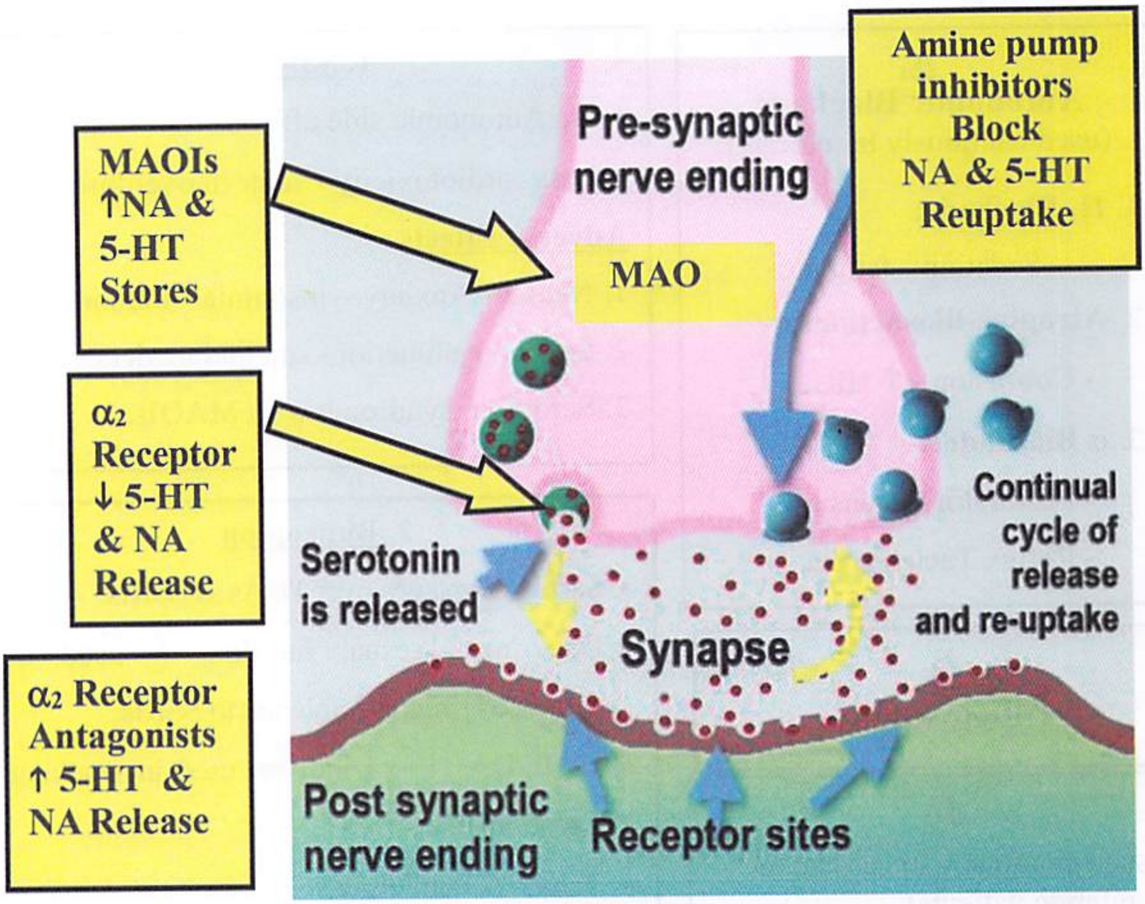
1. Increase in brain biogenic amines (immediately within 12 hours).
2. Downregulation of brain β & 5-HT_2 receptors (delayed for 2-4 weeks).
3. Affect neurotrophic factors essential for survival & function of neurons.

Mechanisms of Increase of Biogenic Amines by Antidepressants

Amine Pump Inhibitors	**MAO Inhibitors**	**Presynaptic α_2 Blockers**
Inhibit uptake I of biogenic amines into neurons resulting in their accumulation in synaptic cleft, potentiating their action at post synaptic receptors.	Inhibit metabolism of biogenic amines by MAO enzyme inside nerve endings → ↑ stores available for release.	↑ NA & 5-HT release into synaptic cleft by preventing α_2 auto-inhibition.
Members 1. **TCAs:** Imipramine - amitriptyline Clomipramine. 2. **SSRI:** Fluoxetine – sertraline Escitalopram. 3. **NDRI:** Bupropion. 4. **SNRI:** Venlafaxine - duloxetine.	**Members** **1. Nonselective** Tranylcypromine. Phenelzine **2. Selective on MAO-A** Moclobemide.	**Members** Mirtazapine (NaSSA)

N.B.:

- **Tricyclics;TCAs:** Block NE & 5HT uptake & autonomic receptors (**H_1, M, α**).
- **SNRIs:** Serotonin Norepinephrine Reuptake Inhibitors.
- **SSRIs:** Selective Serotonin Reuptake Inhibitors.
- **NaSSA:** Noradrenergic and Specific Serotoninergic Antidepressant
- **NDRI:** DA, NA reuptake Inhibitors.


MAOIs
↑NA &
5-HT
Stores
α2
Receptor
↓ 5-HT
& NA
Release
α2 Receptor
Antagonists
↑ 5-HT &
NA Release
Pre-synaptic
nerve ending
MAO
Amine pump
inhibitors
Block
NA & 5-HT
Reuptake
Serotonin
is released
Synapse
Continual
cycle of
release
and re-uptake
Post synaptic
nerve ending
Receptor sites

Mechanism of Action of Antidepressants

Adverse Effects of TCAs

(Limit their use)

A.

Autonomic Blockade

(used cautiously in elderly)

1. **H_1 Blockade:**
   - Sedation - fatigue.
2. **Atropine-like actions:**
   - Confusion - ↑ HR…….
3. **α Blockade:**
   - Postural hypotension.
   - Reflex Tachycardia.

B.

↑ Body weight.

C.

(Used cautiously in cardiac & epileptic patients):

1. Cardiotoxic
   - Conduction defects.
   - Arrhythmias.
2. Convulsions:
   In susceptible patients

S.

(Used cautiously in suicidal or bipolar patients)

1. Safety margin is low.
2. Switch to mania.
3. Sexual dysfunction.
4. Serious drug interactions

Advantages of Newer Antidepressants

(Developed to ↓ side effects of TCAs)

1. SSRIs

- No Autonomic side effects.
- Less cardiotoxicity - safer in overdose.

Adverse Effects

1. Nausea- Anxiety – insomnia - tremors.
2. Sexual dysfunction- suicidal tendency??
3. Serotonin syndrome with MAOIs.

2. Bupropion

- Same advantages over TCAs as SSRIs.
- Does not ↓sexual function → used in depressed patients intolerant to SSRIs.
- ↑ NE/DA (↓ craving) → used in smoking cessation.
- ↑ Risk of convulsions.

3. Venlafaxine (SNRIs)

- No Autonomic side effects.

Adverse Effects

- Nausea- dry mouth- Hypertension.

4. Mirtazapine

- More rapid effect with less nausea & sexual dysfunction→ useful in patients intolerant to sexual dysfunction of SSRIs.
- H_1 antagonist → sedation & weight gain.

Drug interactions with TCA:

- Alcohol- anesthetics → sedation.
- Hypotensive drugs (potentiate postural hypotensive effects of TCAs).
- TCAs potentiate directly acting symapthomimetics (inhibit uptake of biogenic amines).
- Not to be given with MAOIs.

TCAs Toxicity:

- Atropine toxicity- Convulsions
- Conduction block & arrhythmia- hypotension.

Management: $NaHCO_3$ for hypotension & arrhythmia.

MAOIs

- MAOIs were among the earliest antidepressants introduced for therapy of depression but due to their toxicity & serious food & drug interactions, their use is limited & several precautions have to be taken during their administration.

Serious Food (cheese)[19] & Drug Interactions of MAOIs

MAOIs Plus			
Tyramine - rich food	**Cold Remedies** (sympathomimetics)	**TCAs** (→↑ CA)	**SSRIs** →↑ 5HT **Pethidine** →↑norpethidine[20] →↑ 5HT
↓	↓	↓	↓
Hypertensive crisis **(Cheese reaction)**	Hypertensive Crisis.	-Hypertension -Convulsions -Hyperthermia	**"Serotonin syndrome":** - Convulsions -Hyperthermia

---

[19] **Cheese Reaction**: Tyramine in food is metabolized in GIT by MAO-A & MAO-B. MAOIs allow tyramine in tyramine-rich food (old cheese, chicken liver, chocolate) to escape metabolism & release ↑ ↑ ↑ amounts of catecholamines from neurons → hypertensive crisis.

[20] Inhibition of pethidine metabolism by MAOIs →↑formation of neuro toxic metabolite, norpethidine.

Precautions with MAOIs

- Patients on nonselective MAOIs should be warned against serious drug interactions & should be given a list of the foods they should avoid.
- Patients on MAOIs should not receive TCAs or SSRIs except after 2 weeks from stopping MAOIs (effect persists for 2 weeks).
- Avoid in the elderly → postural hypotension - atropine-like actions.

Reversible Inhibitors of MAO-A (RIMA)

- Antidepressant activity of MAOIs is related to inhibition of MAO-A enzyme (responsible for NE & 5HT metabolism). Thus to reduce risk of cheese reaction, selective inhibitors of MAO-A were developed:

Moclobemide

- Short-acting, reversible inhibitor of MAO-A (RIMA).
- Has the advantage of a reduced risk of cheese reaction due to:
  - ☐ **Selective MAO-A inhibitor** → allows MAO-B to metabolize tyramine.
  - ☐ **Short-reversible** MAO-A **inhibitor** → easily displaced by tyramine allowing tyramine to be metabolized by MAO- A.

Other Antidepressants

Agomelatine

- Melatonin M1 and M2 receptor agonist and exhibits 5-HT2C antagonism (↑ DA &NA).
- Used in severe depression: corrects disturbances in sleep circadian rhythm associated with depression.
- Hepatotoxic

Therapeutic Uses of Antidepressants

1. Major depression disorder (**main use**)
2. Anxiety disorders: generalized anxiety disorder -panic disorder -phobias – obsessive compulsive disorders (SSRIs, clomipramine).
3. Post-traumatic stress disorder.
4. Pain disorders: e.g. chronic neuropathic pain (TCA & SNRIs)[21].
5. Urinary incontinence (duloxetine), nocturnal enuresis (imipramine; anticholinergic → contracts urethral sphincter),
6. Eating Disorders: Anorexia Nervosa & Bulimia Nervosa [22](SSRIs &TCAs).
7. Smoking cessation (bupropion).

Guidelines for the use of antidepressants

- Antidepressant effect is delayed for 2 -4 weeks; treatment is continued for 4 weeks before considered unsuccessful. If partial improvement occurs continue for another 4 weeks.
- Following remission, continue treatment for 6 months. Long term maintenance therapy for 2 years may be needed if patient experiences recurrent episodes.
- Gradual withdrawal over 4 weeks.
- SSRIs are the most widely used initial therapy[23].
- In cases resistant to initial therapy switch to a different member of same class or to another class.
- TCAs are reserved for resistant cases due to toxicity & drug interactions.

---

[21] Pain (in the form of pins & needles or electrical shock), due to affection of sensory nerves(of pain, touch, heat & cold) e.g. trigeminal neuralgia, diabetic neuropathy or herpes zoster. Corticospinal monoaminergic pathway is important for pain transmission; thus antidepressants that ↑monoamines possess analgesic activity independent of effects on mood.

[22] Recurrent attacks of excessive appetite resulting in uncontrolled overeating followed by sense of guilt with deliberate vomiting or using laxatives to prevent weight gain.

[23] Sertraline, escitalopram, followed by mirtazapine & venlafaxine have better risk benefit profiles than other antidepressants.

  - Due to toxicity & serious food & drug interactions, MAOIs are reserved for atypical depression associated with anxiety - phobias – obsessions, panic attacks & 2nd choice in refractory major depression.
- Atypical antipsychotic, lithium, or T3 may be added in resistant cases.
- Antidepressants are used in anxiety disorders together with a BZD to calm the patient until the antidepressant becomes effective.

ANTIPSYCHOTIC DRUGS (NEUROLEPTICS)

- Antipsychotics are drugs used to control manifestations of psychosis.

Manifestations of Psychosis (mind is separated from reality)

1. Hallucinations (perception without stimulus) : e.g. auditory (most frequent), visual, tactile....
2. Delusions (False fixed beliefs): e.g. paranoid (suspicious) persecution (people are conspiring against him), grandeur (believes he is a genius).
3. Incoherent speech & abnormal behavior (aggression, agitation).

Schizophrenia (most common & most classic example of psychosis)

- Schizophrenia results from ↑ DA activity in brain mesolimbic system.
- Positive symptoms: Hallucinations, delusions and disorganized behavior.
- Negative symptoms: (4A) Affect flattening (flat emotions), Alogia (decrease speech), Anhedonia, Amotivation & social withdrawal & intellectual dysfunction.

Mechanism of Action of Antipsychotics

- All anti psychotics block D_2 receptors in the mesolimbic system.
- Effect is delayed for several weeks → ↓ patient compliance.

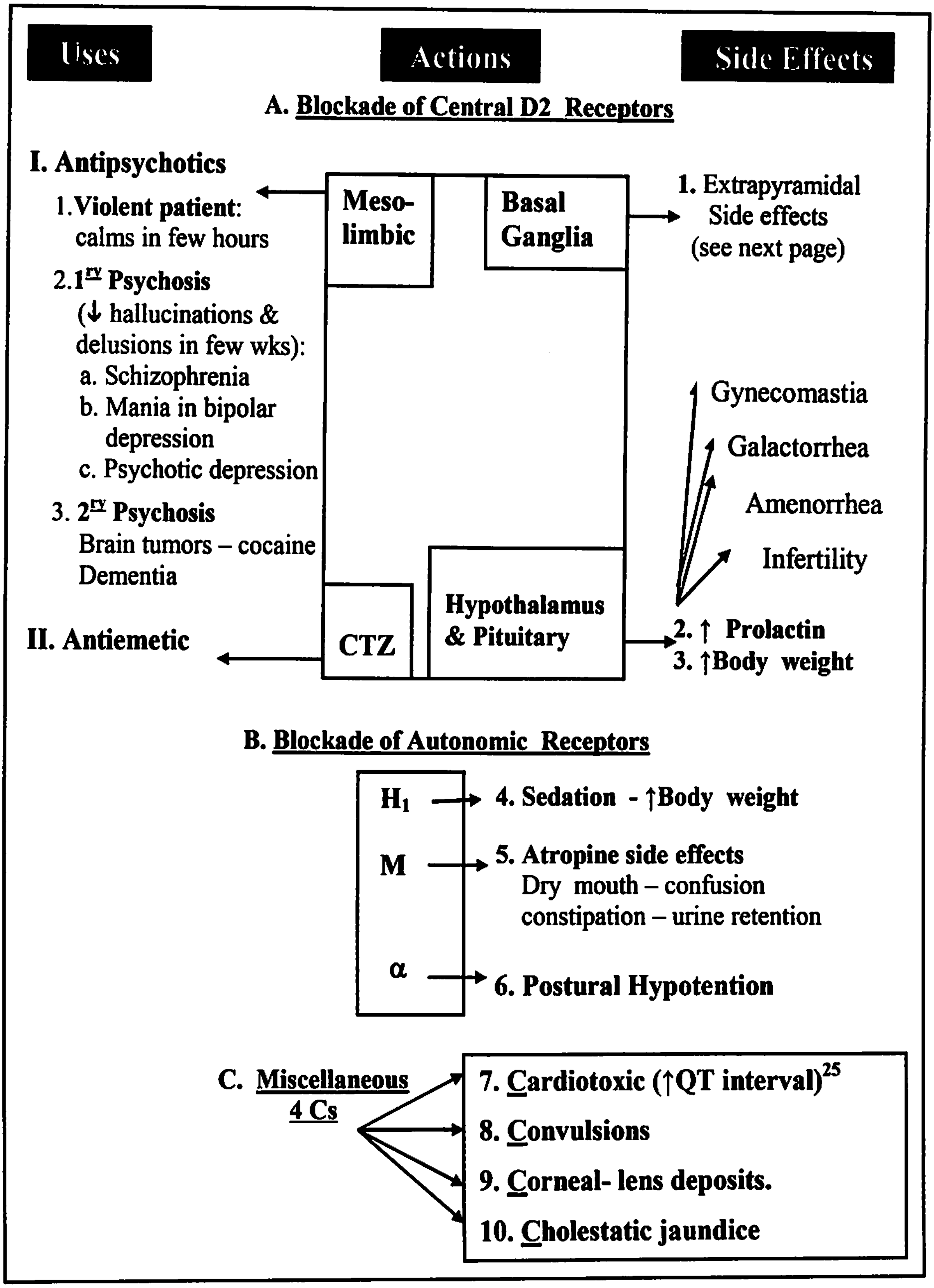
Classification of Antipsychotic Drugs [24]

Typical	Atypical
DA Antagonists	**5HT/DA Antagonists**
Chlorpromazine (prototype) -Thioridazine	Risperidone - Aripiprazole
Haloperidol - Trifluperazine	Clozapine - Olanzapine.

---

[24] Typical agents have a high DA to 5HT blocking ratio. Atypical agents block 5-HT_2 receptors with equal efficacy as D_2 receptors.
Other atypical agents: quetiapine - ziprasidone.

Typical Antipsychotics



Uses **Actions** **Side Effects**

A. **Blockade of Central D2 Receptors**

I. Antipsychotics

1. **Violent patient:** calms in few hours
2. 1^{ry} **Psychosis** (↓ hallucinations & delusions in few wks):
   - a. Schizophrenia
   - b. Mania in bipolar depression
   - c. Psychotic depression
3. 2^{ry} **Psychosis** Brain tumors – cocaine Dementia

II. Antiemetic

Meso-limbic

Basal Ganglia

CTZ

Hypothalamus & Pituitary

1. Extrapyramidal Side effects (see next page)

Gynecomastia

Galactorrhea

Amenorrhea

Infertility

2. ↑ Prolactin
3. ↑Body weight

B. **Blockade of Autonomic Receptors**

H_1 → 4. Sedation - ↑Body weight

M → 5. Atropine side effects
Dry mouth – confusion
constipation – urine retention

α → 6. Postural Hypotention

C. **Miscellaneous**
4 Cs

7. Cardiotoxic (↑QT interval)[25]
8. Convulsions
9. Corneal- lens deposits.
10. Cholestatic jaundice

---

[25] ↑QT interval occurs especially with thioridazine which also causes retinal deposits.

Extrapyramidal Side Effects

Disorder	Features	Mechanism	Management
1. **Akathesia**	Motor restlessness	Due to blockade of D_2 receptors in basal ganglia	Anticholinergics, e.g. benztropine may be given routinely with antipsychotics as prophylaxis against extrapyramidal side effects but may exacerbate tardive dyskinesia
2. **Dystonia**	Muscle spasm, e.g. neck torticollis		
3. **Parkinsonism**	Rigidity Hypokinesia Tremors	Blockade of D_2 receptors in basal ganglia → relative↑ in cholinergic activity ↓ ---------------- ↑ DA ACh **Relieved by anticholinergics**	
4. **Tardive dyskinesia** (late, after 2-5 years)	Abnormal involuntary movements: - chewing - sucking - "fly – catching" movement of tongue	Supersensitivity of DA receptors following chronic blockade ↑↑↑---------------↓ DA ACh **Exacerbated by anticholinergics**	**Preventive:** - Least possible dose of antipsychotics - Minimal duration - Avoid routine use of anticholinergics - Switch to atypical agents

N.B: Neuroleptic malignant syndrome (rare)

- Muscle rigidity, fever & labile blood pressure followed by a severe form of parkinsonism. It is due to rapid blockade of central DA receptors in patients sensitive to extrapyramial effects of neuroleptics (idiosyncrasy).
- Management: muscle relaxants (diazepam or dantrolene)- antiparkinsonian drugs (bromocriptine).

Classification of Typical Antipsychotics

(Equal in efficacy but differ in potency & side effects)

A. Low potency

Chlorpromazine - Thioridazine

- Less central side effects.
- More autonomic & miscellaneous side effects.

B. High potency

Haloperidol -Trifluperazine

- More central side effects.
- Less autonomic & miscellaneous side effects → preferred in elderly & cardiac patients.

II. Atypical Antipsychotics

- Block 5-HT$_2$ receptors with equal efficacy as D$_2$ receptors.
- Possess central, autonomic & miscellaneous side effects (see before).

Advantages over typical agents

1. **Less central side effects** (more selectivity on mesolimbic system)
    - Less Parkinsonism - akathesia - dystonia - tardive dyskinesia[26]
    - Less galactorrhea & gynecomastia (except with resperidone).
2. **More efficacy** (due to more 5-HT antagonism)
    - Improve negative symptoms; typical agents control only positive symptoms.
    - Clozapine is effective in resistant cases (30% of cases) → reserved for these cases only due to ↑ risk of agranulocytosis & seizures.

---

[26] This advantage is lost with aripiprazole and high dose risperidone (> 6mg).

Special features of some important members[27]

Risperidone: Less extrapyramidal & autonomic side effects, less weight gain.

But, may induce galactorrhea & gynecomastia and ↑QT interval.

Clozapine: Less central side effects.

↑ Autonomic side effects.

↑ Body weight - insulin resistance- hyperlipidemia.

↑ Risk of seizures.

Agranulocytosis

Olanzapine: Similar to clozapine with no agranulocytosis.

Aripiprazole: - Has extrapyramidal side effects

-Favorable effect on cognitive function (preferred in children)

-Lesser effect on body weight & lipids (preferred in obese patients).

---

[27] Quetiapine: ↑ sedation, less weight gain, ↑QT interval.
Ziprasidone: ↓ autonomic effects, less weight gain, ↑QT.

LITHIUM CARBONATE

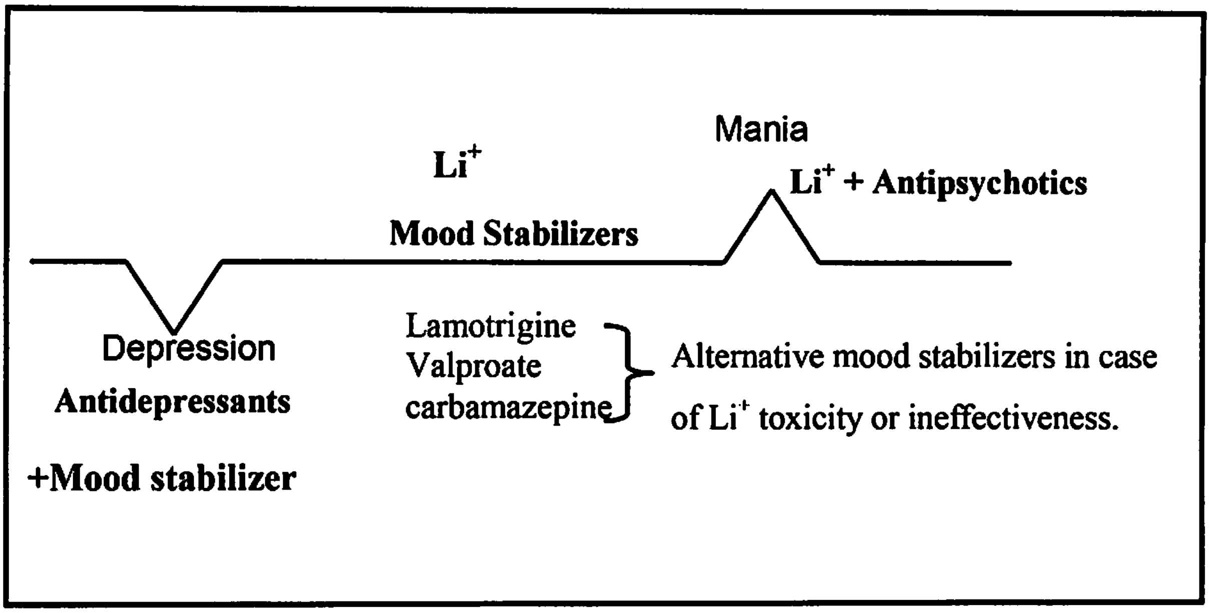
- Monovalent cation similar to Na.
- Mainly used in bipolar manic depression as:
  1. **Mood stabilizer:**

     ↓ Mood swings (maintenance therapy).
  2. **Anti manic:**

     ↓ Manic behavior in manic phase (antipsychotics are added for rapid control of severe mania since the effect of lithium is delayed for several weeks).
- **Other uses** :
  1. Recurrent endogenous depression.
  2. Adjunct to antidepressants in refractory unipolar depression.

N.B.:

- The first-line treatment for bipolar depression is lithium or lamotrigine (Mood stabilization and antidepressant effects).
- Antidepressants monotherapy is not recommended, given the risk of switch into mania. Therefore, they are only used simultaneously with mood stabilizer (lithium) in severe bipolar depression.


Mania
Li^+
Li^+ + Antipsychotics
Mood Stabilizers
Depression
Antidepressants
+Mood stabilizer
Lamotrigine
Valproate
carbamazepine
Alternative mood stabilizers in case of Li^+ toxicity or ineffectiveness.

Drug Treatment of Bipolar Manic Depression

Adverse Effects, Toxicity & Precautions of Lithium

Adverse Effects	Precautions
1. CNS: fine tremors. **2. GIT:** nausea - vomiting - diarrhea.	• Coarse tremors & ↑GIT symptoms are early warning signs of toxicity.
3. Renal: - Antagonizes ADH: polyuria → thirst. - Nephrogenic diabetes insipidus. - Renal tubular damage.	• Monitor kidney function.
4. Thyroid : Benign enlargement with or without hypothyrodism.	• Monitor thyroid function.
5. Toxic drug : a) Narrow TI (0.6-1.5 mEq/l). b) Long $t_{½}$. c) Cumulative.	• Monitor Li^+ serum level. • Adjust dose in reduced Li^+ excretion, as in: 1. Na^+ depletion by diuretics. 2. Renal dysfunction. 3. Old age (↓ renal function).

Lithium Toxicity

- Serum Li^+ level > 2 mEq/l.

Manifestations

- Vomiting - diarrhea - coarse tremor (early signs of toxicity).
- Ataxia - arrhythmia.
- Confusion - convulsions - coma.

Management

- Fluids for dehydration- hemodialysis.
- Na HCO_3 → ↓ Li^+ reabsorption[28].

---

[28] Li+ is excreted unchanged renally. Li+ competes with Na+ for tubular reabsorption; therefore:-
Na^+ depletion (e.g. by diuretics) → ↑ Li^+ reabsorption →↑ serum Li^+ level → Li^+ toxicity.
-Na^+ loading → ↓ Li^+ reabsorption → ↑renal excretion → useful in treatment of toxicity.

DRUG THERAPY OF EPILEPSY

Definition of Epilepsy

- Chronic disease characterized by repeated attacks (seizures or fits) of abnormal electrical discharge of cerebral neurons resulting in EEG, motor, sensory, autonomic or psychological changes.

Etiology

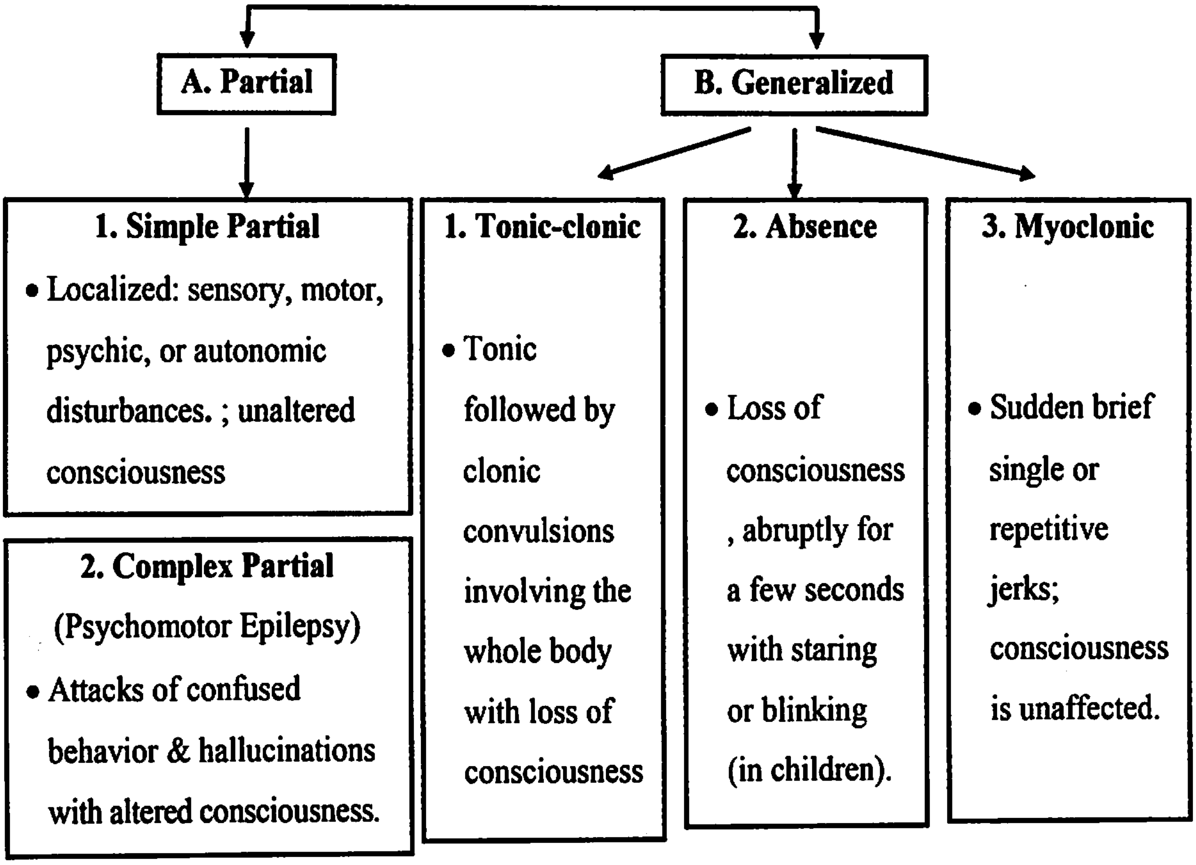
A. Primary epilepsy (unknown cause, i.e. idiopathic).

B. Secondary epilepsy caused by:

1. Trauma, meningitis, brain tumors, fevers, hypoglycemia.
2. Drugs: insulin (hypoglycemia) - TCAs – cocaine- antipsychotics – Li^+.

Classification of Epilepsy

- Epilepsy is caused by a group of hyper excitable neurons with excessive electrical discharge which might be localized (partial) or spread (generalized).



A. Partial

- **1. Simple Partial**
  - Localized: sensory, motor, psychic, or autonomic disturbances. ; unaltered consciousness
- **2. Complex Partial** (Psychomotor Epilepsy)
  - Attacks of confused behavior & hallucinations with altered consciousness.

B. Generalized

- **1. Tonic-clonic**
  - Tonic followed by clonic convulsions involving the whole body with loss of consciousness
- **2. Absence**
  - Loss of consciousness , abruptly for a few seconds with staring or blinking (in children).
- **3. Myoclonic**
  - Sudden brief single or repetitive jerks; consciousness is unaffected.

Antiepileptic Drugs

Members

I. Classic agents (major or older agents)

- Phenytoin (prototype) – carbamazepine – valproate (valproic acid) - ethosuximide.
- Phenobarbital - benzodiazepines.

II. Newer agents[29]

- Lamotrigine – levetiracetam – oxcarbazepine.
- Topiramate – gabapentin- pregabalin.

Mechanism of Action

- Anti-epileptics block initiation or spread of seizures by ↓ hyper-excitability of cerebral neurons by acting on neurotransmitters or by blocking ion channels.
- Most antiepileptic drugs act by more than one mechanism:

1. **Blockade of Na^+ Channels** [30]→↓ repetitive firing of neurons
    - Phenytoin – carbamazepine – valproate.
    - Topiramate - lamotrigine.
2. **Blockade of T- type Ca^{++} Channels in thalamus** → ↓ brain rhythmic activity (effective in absence seizures)
    - Ethosuximide.
    - Valproate.
3. **Blockade of presynaptic voltage gated Ca^{++} Channels** → ↓glutamate release
    - Lamotrigine.
    - Gabapentin – pregabalin.
4. **Binding to vesicle protein VS2A**→ modify release of glutamate
    - Levetiracetam.

---

[29] Newer agents: - lacosamide - zonisamide- rufinamide- felbamate, vigabatrin- tiagabine, preampenel.

[30] Other Na channel blockers: lacosamide - zonisamide- rufinamide.

5. **NMDA glutamate receptor antagonists**[31]

- Valproate.

6. **Effects on GABA**

i. **Facilitate GABA Action**: phenobarbital –benzodiazepines –topiramate.

ii. ↑ **GABA Level**[32]: inhibits breakdown by transaminase: valproate.

7. **Acetazolamide:**

- Antiepileptic effect is due to metabolic acidosis, but tolerance occurs.

Therapeutic Uses

1. Epilepsy: (see below).
2. Mood stabilizers in bipolar depression:
   - Lamotrigine – valproate – carbamazepine.
3. Neuropathic pain (trigeminal neuralgia, post herpetic & diabetic neuralgia):
   - Carbamazepine- gabapentin - pregabalin.
4. Migraine:
   - Valproate - topiramate.
5. Antiarrhythmic:
   - Phenytoin.

---

[31] Other NMDA antagonists: felbamate, preampenel.

[32] Tiagabin: inhibits GABA uptake, vigabatrin inhibits GABA breakdown by transaminase .

Choice of Antiepileptic Drugs in Different Types of Epilepsy

Partial[33]	Tonic- clonic[34]	Absence[35]	Myoclonic[36]
First line			
• Carbamazepine • Lamotrigine.	• Valproate. • Lamotrigine.	• Ethosuximide. • Valproate	• Valproate.
Alternatives			
• Levetiracetam • Valproate • Oxcarbazepine	• Carbamazepine. • Oxcarbazepine	• Lamotrigine.	• Levetiracetam • Topiramate.

N.B.:

- Valproate is preferred to ethosuximide if tonic- clonic or myoclonic seizures coexist.
- Phenytoin is used in parial & generalized tonic-clonic (due to troublesome pharmacokinetics & cosmetic disturbances, other agents are prefferred). Not used in absence seizures (may exacerbate seizures).
- Oxcarbazepine:related to carbamazepine; alternative in partial & tonic clonic seizures.
- Acetazolamide: is used in premenstrual fits (no tolerance occurs since it is used intermittently).
- Due to sedation & tolerance, phenobarbital & BZD are used mainly in acute fits & in status epilepticus. Phenobarbital (in tonic-clonic & partial) & clonazepam (in absence & myoclonic) are used as 2nd line or adjuncts to other agents.

---

[33] Adjunctive treatment (if first line treatment is not effective or not tolerated): carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate, topiramate

[34] Adjunctive treatment: clobazam, lamotrigine, levetiracetam, valproate, topiramate

[35] Adjunctive treatment :combination of ethosuximide, lamotrigine or valproate.

[36] Adjunctive treatment :levetiracetam, valproate, topiramate

Adverse Effects & Precautions of Major (classic) Anti-epileptics

	Phenytoin	Carbamazepine	Valproate
Hypersensitivity	Skin rash → stop drug		
GIT Disturbances	Nausea - vomiting - epigastric pain (most common with valproic acid) → give small dose after meals.		
Neurological Disturbances (specially in toxic doses)	• Nystagmus, diplopia. • Ataxia. • Drowsiness. • ↓ Learning in children.	• Diplopia. • Ataxia. • Drowsiness.	• Fine hand tremors. • Ataxia. • Less sedative.
Effects on Hepatic Microsomal Enzymes (monotherapy is preferred)	**Enzyme inducer** • ↑ Metabolism of other antiepileptics. • **Osteomalacia:** ↑ vitD metabolism (→ vit D & Ca^{2+} supplements).	**Enzyme inducer** • ↑ Metabolism of antiepileptics , warfarin & other drugs.	**Enzyme inhibitor** • ↓ Metabolism of antiepileptics & other drugs.
Hematological Effects (→regular blood picture)	• Megaloblastic anemia 'supplement folic acid' • Lymphadenopathy	• Leukopenia • Agranulocytosis	• Thrombocytopenia
Teratogenicity → give folic acid	• Cleft palate & lip - heart anomalies.	• Less teratogenic .	• Spina bifida. • Neural tube defect.
Others	1. **Cosmetic changes** • Gingival hyperplasia (→gum hygiene). • Coarse facial features. • Hirsutism - acne. 2. **Unpredictable serum level→** monitor serum level.	• Water intoxication & dilutional hyponatremia (potentiates ADH).	• **Hepatotoxicity** (rare but fatal). • Hair loss. • ↑ Appetite. • ↑ Body weight.

N.B.: **Ethosuximide** (safest): GIT upset, skin rash, dizziness, drowsiness, headache.

Specific adverse effects of newer antiepileptics[37]

- Newer agents are generally better tolerated with fewer drug interactions than the older agents. Specific adverse effects include:
  - **Lamotrigine**: rash → fatal dermatitis (stevens johnson syndrome), hypersensitivity.
  - **Topiramate**: renal stones- myopia (→glucoma)- weight loss- hypohydrosis.
  - **Levetiracetam**: mood & behavioral changes.
  - **Gabapentin /Pregabalin**: sedation, ataxia, weight gain- peripheral edema.

General guidelines for antiepileptic drug therapy

1. **Proper diagnosis** of type of epilepsy & prescribing the appropriate drug (wrong choice may worsen the condition).
2. **Monotherapy** is preferred since anti-epileptics are either enzyme inducers (phenytoin, carbamazepine & phenobarbital) or enzyme inhibitors (valproate). Combinations could result in changes in serum level of drugs.
3. **Start therapy with a small dose & a single drug** and gradually ↑ dose. If no effect is noted, **gradually** substitute or add another drug.
4. **Long duration of treatment**: If epileptic fits are absent for 2 years, consider terminating therapy; but if fits recur, repeat treatment for another 2 years.
5. **Gradual drug withdrawal:** over 6 months to avoid status epilepticus or relapse.
6. **Folic acid supplements:** especially in child bearing period to ↓ teratogenic risk.

---

[37] Zonisamide: rash -renal stones- weight loss- hypohydrosis

Oxcarbazepine: hyponatremia, rash

7. **Pregnancy & child bearing period**: Be aware of potential effect of valproate in pregnancy. Pregnant females should receive the lowest effective dose of the drug (do not stop drug as seizures may be harmful to fetus).Pregnancy ↑ metabolism of anti-epileptics → adjust dose. Anti-epileptics may reduce efficacy of contraceptives.
8. **Periodic monitoring of serum level of drugs**, since a drop below therapeutic level →loss of seizure control while an increase in level →toxicity (CNS depression → stupor - coma - respiratory depression).
9. The use of phenytoin is limited due to its troublesome kinetics resulting in unpredictable serum level due to:
    a. Irregular bioavailability (→use one formula from a single manufacturer).
    b. Saturation kinetics (serum conc. may↑ to toxic levels → monitor serum level).
    c. Drug interactions if combined with other antiepileptics.
10. Sedation & tolerance limit the use of phenobarbital & clonazepam.

Management of Status Epilepticus[38]:(drugs are given IV)

1. Lorazepam[39], midazolam or diazepam (IV or rectal) → for rapid control.
2. Fosphenytoin[40] or phenytoin → long-acting, to maintain control.
3. Phenobarbital →2nd choice to phenytoin.
4. IV anesthesia → in resistant cases.

---

[38] Continuous or repetitive seizures with impaired consciousness in-between fits.

[39] Preferred to diazepam as its antiepileptic effect is longer & it is non irritant to veins.

[40] Fosphenytoin: soluble, prodrug, safer than pheytoin (no need for the cardiotoxic solubilizing agent propylene glycol).

Antiparkinsonian Drugs

Definition

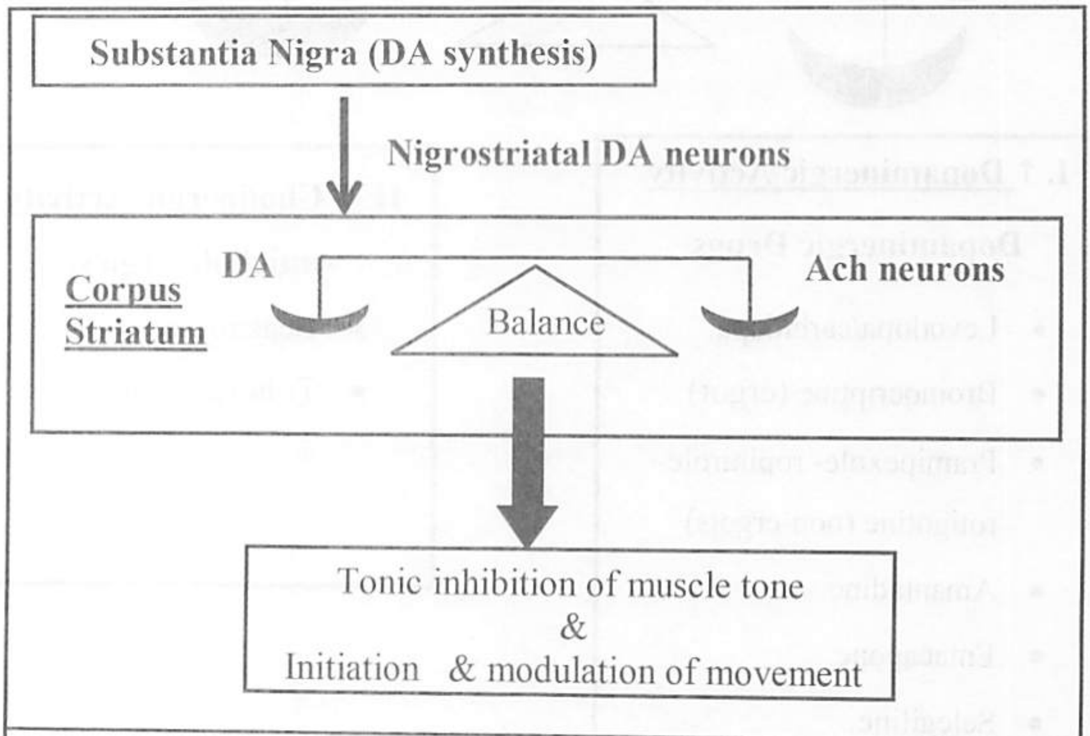
- Parkinson's disease is a slowly progressive neurological disease resulting from degeneration of nigrostriatal DA neurons & characterized by tremors at rest, rigidity, bradykinesia & postural instability.

Causes of Parkinsonism (most common in the elderly)

1. **Idiopathic (Parkinson's disease):**

   Due to unknown neurotoxin or oxidation reactions with free radical generation → neuronal degeneration (environmental & genetic factors may be responsible).

2. Viral encephalitis - CO or manganese poisoning.
3. Drug-Induced Parkinsonism:
   - **Antipsychotics** → block D_2 receptors.
   - **Reserpine** → depletes DA stores.
   - **Methyldopa** → inhibits DA synthesis.

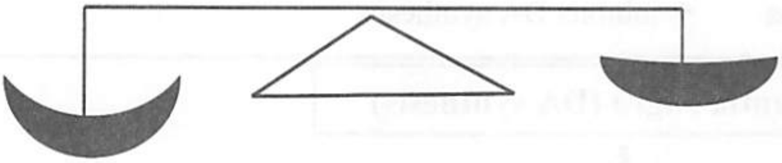

Substantia Nigra (DA synthesis)
Nigrostriatal DA neurons
Corpus Striatum
DA
Balance
Ach neurons
Tonic inhibition of muscle tone
&
Initiation & modulation of movement

DA /Ach Balance in Basal Ganglia

Pathophysiology of Parkinson's disease (see previous fig.)

- The basal ganglia exert a tonic inhibitory effect on muscle tone & are responsible for proper initiation & modulation of movement.
- These effects require a normal balance in the basal ganglia between Ach & DA.
- In the basal ganglia, DA is synthesized in the substantia nigra & reaches the corpus striatum through the nigrostriatal DA neurons.
- In Parkinson's disease, degeneration of nigrostriatal DA neurons → ↓ striatal DA & dominance of cholinergic system resulting in:
  1. Bradykinesia or akinesia (failure to initiate movement).
  2. Tremors.
  3. Rigidity (involuntary contractions of all muscles due to loss of tonic inhibition of muscle tone).

Antiparkinsonian Drugs aim to restore DA/Ach balance



I. ↑ Dopaminergic Activity

Dopaminergic Drugs

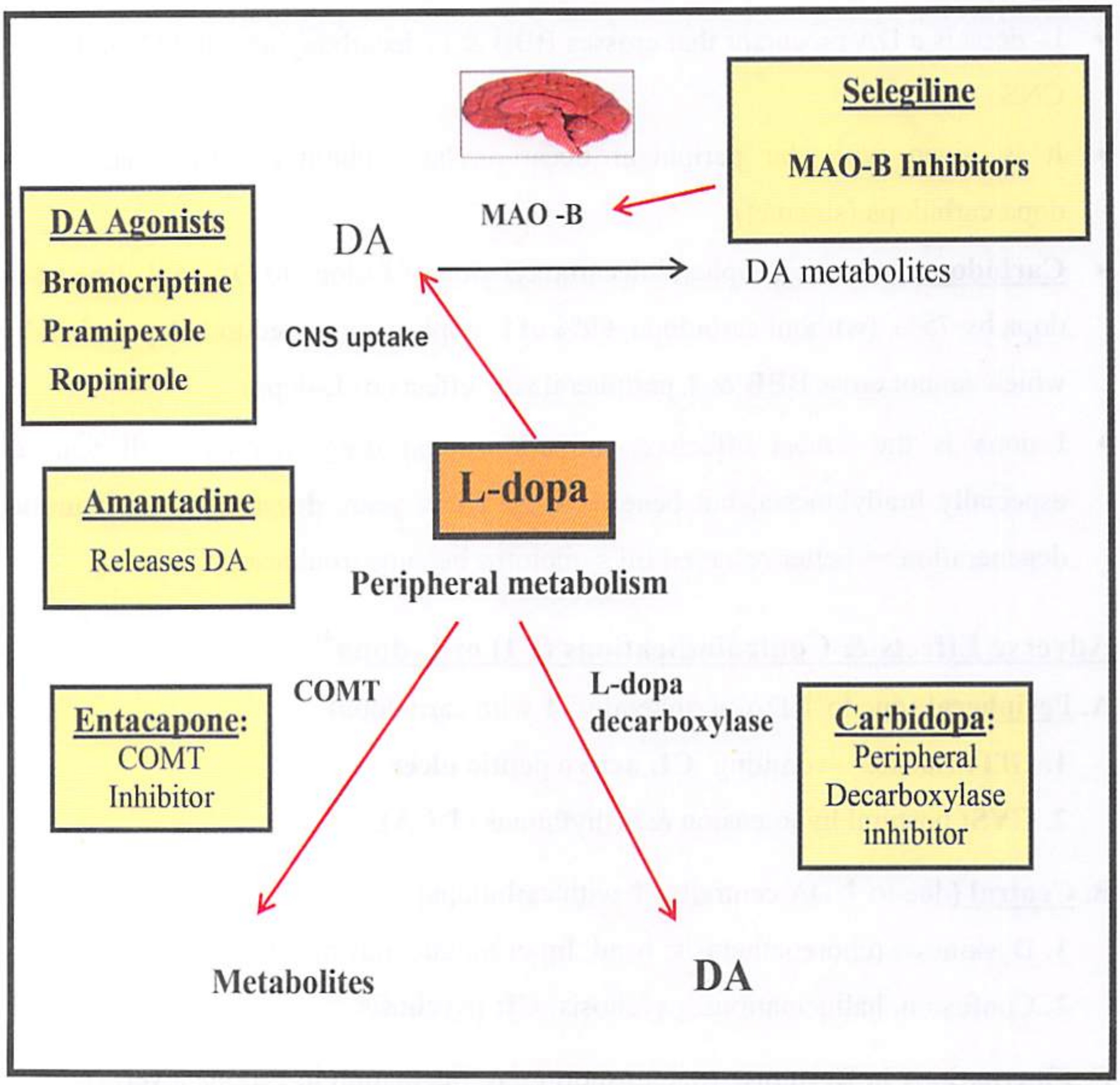
- Levodopa/carbidopa.
- Bromocriptine (ergot)
- Pramipexole- ropinirole- rotigotine (non-ergots)
- Amantadine.
- Entacapone.
- Selegiline.

II. ↓ Cholinergic Activity

Anticholinergics.

- Benztropine
- Trihexphenidyl

II. Dopaminergic Drugs


Selegiline
MAO-B Inhibitors
DA Agonists
Bromocriptine
Pramipexole
Ropinirole
DA
MAO -B
DA metabolites
CNS uptake
Amantadine
Releases DA
L-dopa
Peripheral metabolism
COMT
L-dopa decarboxylase
Entacapone: COMT Inhibitor
Carbidopa: Peripheral Decarboxylase inhibitor
Metabolites
DA

Site of action of Antiparkinsonian Dopaminergic Drugs

(DA is not used as it cannot cross BBB)

Levodopa (L-dopa)

(Mainstay of Therapy)

- L- dopa is a DA precursor that crosses BBB & is decarboxylated to DA in the CNS.
- It is given with the peripheral decarboxylase inhibitor, carbidopa, as L-dopa/carbidopa (sinemet).
- **Carbidopa** prevents peripheral decarboxylation of L-dopa to DA → ↓ dose of L-dopa by 75%. (without carbidopa, 99% of L-dopa is converted to DA peripherally which cannot cross BBB & ↑ peripheral side effects of L-dopa).
- L-dopa is the most effective antiparkinsonian drug; improves all features especially bradykinesia, but benefits ↓ in a few years due to gradual neuronal degeneration → better reserved till symptoms become troublesome.

Adverse Effects & Contraindications (CI) of L-dopa[41]

A. **Peripheral** (due to ↑ DA peripherally; ↓ with carbidopa)

1. **GIT:** Nausea – vomiting **CI: active peptic ulcer**.
2. **CVS:** postural hypotension & arrhythmias (↑ CA).

B. **Central** (due to ↑ DA centrally; ↑ with carbidopa)

1. Dyskinesia (choreoathetosis; head, lip or tongue movements).
2. Confusion, hallucinations; psychosis; **CI: psychosis**.

C. **Fluctuations in Response** (due to short t ½ & fluctuation in L-dopa level??)

1. On-off effect (sudden swings from mobility to bradykinesia).
2. End-of-dose akinesia: gradual loss of effect (wearing off) before next dose.

N.B.:

- Domperidone → ↓ L-dopa- induced nausea & vomiting (blocks peripheral D_2 receptors in CTZ (outside BBB) but not central D_2 receptors in basal ganglia (doesn't cross BBB) → doesn't interfere with anti-parkinsonian effect of L-dopa).

---

[41] Other side effects: activation of malignant melanoma & mydriasis; CI: narrow angle glaucoma.

Other Dopaminergic Drugs Used in Parkinsonism

Drug	Mechanism of Action	Adverse Effects
I. Pramipexole **Ropinirole** **Bromocriptine**	• Direct D_2 agonists. (Less fluctuation due to rapid absorption - longer $t_{½}$).	• Simialr to L-dopa: Hallucination –dyskinesia. Nausea- postural hypotension • Impulse control disorder[42]. • Day time sleepiness. • Vasospasm & cardiac fibrosis (bromocriptine)
II. Amantadine (Given together with other agents)	• ↑ DA release (mild effect) → enhances L-dopa effect. • Blocks NMDA receptors[43].	- Insomnia - hallucination. - Ankle edema. - Livido reticularis[44].
III. Selegiline[45] (Alone, modest benefit, or adjuncts to L dopa)	• Selective inhibitor of MAO-B → delays breakdown of nigrostriatal DA → prolongs L-dopa action → ↓ fluctuation	- Insomnia (selegiline)[46] - Hallucination. - Very low risk of cheese reaction[47].
IV. Entacapone[48] (adjunct to L dopa)	• COMT inhibitor → ↓ L-dopa peripheral metabolism → ↑ its bioavailability & prolongs its action → ↓ fluctuations.	• Related to L-dopa /carbidopa -Hallucination –dyskinesia. -Nausea- postural hypotension • Orange urine.

---

[42] Compulsive gambling & eating - hypersexuality.

[43] May block glutamate receptor (NMDA) → ↓ glutamate excitotoxicity → ↓ neuronal degeneration.

[44] Purple spotting of skin

[45] Neuroprotective, antioxidant → may ↓ disease progress (more with the MAO B inhibitor rasagiline).

[46] Due to its metabolism to an amphetamine - like substance. Rasagiline is not metabolized to amphetamine like substance → no insomnia).

[47] Selectivity of selegiline is lost at high doses.

[48] Tolcapone (hepatotoxic).

N.B.:

- **Non-ergot DA agonists** (ropinirole, pramipexole): preferable to ergots (bromocriptine → vasospasm, cardiac, pulmonary & retroperitoneal fibrosis).[49]
- **Apomorphine:** DA agonist, rapid and more effective than L-dopa. For "rescue therapy" in patients experiencing sudden akinetic episodes. Can also be given intermittently subcutaneously → ↓'off' time in advanced Parkinson's disease.

II. Anticholinergics

Benztropine - Trihexphenidyl

- Block central cholinergic activity → restore DA/Ach balance.
- Improve tremors (mainly) & rigidity, but less effective on bradykinesia.

Used in:

i. Drug induced Parkinsonism: preferred to dopaminergic drugs, since dopaminergic agents cannot be used in antipsychotic-induced Parkinsonism because DA receptors are blocked by antipsychotics & dopaminergic agents may aggravate the psychotic disorder of the patient.

ii. Parkinson disease (especially in the young): adjuvants to dopaminergic drugs in cases presenting with tremors & to control sialorrhea.

N.B.: may delay gastric emptying → ↓ L-dopa absorption.

Side Effects:

- Similar to atropine but less severe (dry mouth, constipation, confusion……).

Caution in elderly (avoid in patients over 70)

- ↑ Memory loss & hallucinations.
- Urine retention in patients with enlarged prostate.

N.B.: beta adrenergic blockers may be used for tremors.

---

[49] **Rotigotine**: non-ergot DA agonist; skin patch allows more continuous dopaminergic stimulation; given in early Parkinsonism.

I. Choice of drugs in Early Disease[50]

- First choice agents in early Parkinson's disease & motor symptoms include:
  - **L-dopa/carbidopa.**
  - **Non ergot dopamine agonists (oral/transdermal).**
  - **MAO-B inhibitors.**
- L-dopa is the most effective agent for motor symptoms.
- To avoid L-dopa-related motor complications, other agents are used first, in mild cases, or when tremor is the only symptom.
- It is preferred to start therapy with a DA agonist in younger patients (<65 years) & with levodopa in older patients (≥65 years) with troublesome bradykinesia.

Amantadine: is usually used with other agents in young patients but not as first line treatment (tolerance develops in few months).

Anti-cholinergics: should not be used as1st line treatment in Parkinson's but may be added if tremors are troublesome, especially in young patients.

II. Management of motor complications in advanced Parkinson's disease

- L-dopa will eventually be used resulting in motor complications (dyskinesias & fluctuations (end of dose akinesia & on/off effect), which can be managed by:
  - MAO-B inhibitors.
  - DA agonists *(oral or transdermal)*.
  - Intermittent subcutaneous apomorphine (→ ↓'off' time).
  - COMT inhibitors → ↓'off' time in advanced cases with motor fluctuations.
  - Amantadine.

Avoid pyridoxine: ↑ peripheral decarboxylation of L-dopa → ↓ effect.

Diet: low in protein to ↓ fluctuation in L-dopa response (NH_2 acids compete with L-dopa → ↓absorption & CNS uptake). Diet rich in fibers & fluid for constipation.

---

[50] Drugs should not be started until symptoms interfere with daily activities. Therapy with 2 or more agents will eventually be necessary as disease progresses.
Management of psychosis & depression: Low-dose clozapine - antidepressants.
Management of dementia: Rivastigmine.

DRUG THERAPY OF ALZHEIMER'S DISEASE

- Alzheimer disease is the most common cause of dementia in the elderly.
- It is a neurodegenerative disorder characterized by impairment of memory & cognitive function together with behavioral changes (psychosis, depression).
- It may lead to a completely vegetative state and early death.

Pathological changes[51]

- Increased deposits of beta amyloid (Aβ) plaques and intraneural fibrillary tangles of hyperphosphyrlated tau protein in cerebral cortex.
- Amyloid deposits→↑glutamate→activates NMDA receptors → ca^{2+}influx into neurons→ cell apoptosis; exocitotoxity.
- Progressive loss of cholinergic nicotinic neurons involved in cognition & memory.

Aim of therapy

- ↑ Cholinergic activity.
- ↓ Glutamate exocitotoxity.

Mangement

I. Symptomatic treatment:

1. Cholinesterase inhibitors[52]:

- Donepezil
- Rivastigmine: only agent that is available as transdermal patch
- Galantamine.

Mechanism of action:

- ↑ Cholinergic transmission in brain by inhibiting acetylcholinestrase.
- Galantamine: also stimulates presynaptic nicotinic receptors →↑Ach release.

---

[51] Other mechanisms: inflammation, oxidative damage, disturbance in iron & cholesterol metabolism.

[52] Tacrine was the first drug approved for AD. It is rarely used, due to hepatotoxicity.

Characteristic features

- Orally active .
- Adequate CNS penetration; some selectivity to AchE centrally compared to periphery.
- Improve cognitive function but do not delay progress of disease.

Uses:

- Mild to moderate cases of Alzheimer disease.
- Dementia of parkinsonism (only rivastigmine)

Side effects[53]:

1. Cholinomimetic effects: anorexia, nausea, vomiting, diarrhea, bradycardia, tremors, etc....
2. Drug interactions involving CYP 450 (except rivastigmine).

2. NMDA receptor Antagonists: Memantine

Mechanism of action:

- Non competitive antagonist of (NMDA) receptors→ limiting influx of ca^{2+} into neurons →protects neurons from glutamate induced excitotoxicity[54].

Uses:

- Moderate to severe cases.

Side effects: (well tolerated & less toxic than cholinomimetics)

1. Confusion, dizziness, headache, hallucination.
2. Constipation.

II. Other agents (unlabeled use)

- Cholesterol-lowering agents: Statins.
- Insulin sensitizers: PPAR γ agonists (rosiglitazone) - intranasal insulin.
- Anti- inflammatory (NSAIDs) & antioxidants (vitamin E & omega-3 fatty acids (disappointing results, but research continues).

---

[53] Side effects reduced by: gradual titration over > 3 months - transdermal rivastigmine .

[54] It also blocks 5HT3 and nicotinic receptors (unknown role in dementia).

DRUG ABUSE

- Drug abuse is the nonmedical use of any drug (usually psychoactive), that is unacceptable by the society & results in health problems.
- Drug abuse reults in drug dependence due to development of:
  1. **Physical dependence**: Adaptation of body to drug resulting in the necessity to continue using it to avoid a physical withdrawal syndrome on drug withdrawal.
  2. **Craving:** Severe compulsion to take a drug repeatedly to re-experience a pleasant feeling, e.g. euphoria. Addictive drugs activate the mesolimbic dopaminergic reward pathway → ↑DA release → euphoria
  3. **Tolerance**: ↓ Drug response following its continuous use → larger dose is required to produce the same initial effect → loss of control of addict over amount of drug used.

Classification of Drugs of Abuse

I. CNS Depressants:

1. **Sedative hypnotics:** barbiturates - benzodiazepines - alcohol.
2. **Narcotics:** heroin - morphine - pethidine - codeine.

II. CNS Stimulants: caffeine - nicotine - cocaine – amphetamine - khat.

III. Hallucinogens: LSD -mescaline -phencyclidine.

IV. Cannabis.

V. Inhalants: induce euphoria and hallucinations.

1. Solvents in glues & paints (strong dependence).
2. Anesthetics; nitrous oxide & ether (moderate dependence).

Drug abuse occurs more with short-acting agents & withdrawal syndrome is more severe than that following longer-acting agents.

I. Barbiturates (Strong Dependence)

BZDs (Moderate Dependence)

Acute Effects

- Euphoria - relieve anxiety and insomnia.

Risks of Chronic Abuse

- Memory loss.

Withdrawal Syndrome (severe with barbiturates - mild with BZDs)

- Insomnia - anxiety - tremors - delirium - hallucinations - convulsions.

Management of Barbiturates & BZDs Abuse

- Replace short-acting agent by a longer-acting one → less severe withdrawal:
  - ☐ Phenobarbital for pentobarbital.
  - ☐ Diazepam for clonazepam, alprazolam, flunitrazepam.

II. Alcohol

(Strong Dependence)

Mechanism : acts on GABA- A receptor→↑ GABA effect (cross tolerance with BZDs)

Acute Effects

- Euphoria - relaxation - increased self-confidence.

Withdrawal Syndrome

- Similar to barbiturates with **delirium tremens**: delirium - tremors - psychosis (visual hallucinations of crawling bugs).

Risks of Chronic Abuse (Alcoholism)

1. Withdrawn, homicidal or suicidal individual - work & family problems.
2. Liver cirrhosis - peptic ulcer – cardiomyopathy.
3. Dementia - peripheral neuropathy.
4. Thiamine deficiency → Wernicke-Korsakoff syndrome (external eye muscles paralysis, ataxia, confusion, psychosis).

Management of Alcohol Abuse

1. **Diazepam** or **chlordiazepoxide** (longer acting sedatives).
    - a. Replaces alcohol (gradual withdrawal of diazepam is smoother).
    - b. Anticonvulsant (controls convulsions of withdrawal syndrome).
2. Thiamine supplements.
3. Psychotherapy (group therapy) together with drugs to avoid relapse following detoxification:
    - **a. Disulfiram:**
        - Inhibits aldehyde dehydrogenase involved in alcohol metabolism → accumulation of acetaldehyde → nausea & vomiting & flushing (disulfiram - like reaction). To avoid this reaction, patients give up drinking.
    - **b. Naltrexone:** ↓ craving.
    - **c. Acamprosate:** weak NMDA antagonist, GABA A receptor activator.

III. Opioids

(Very Strong Dependence)

Acute Effects

1. Euphoria (rush).
2. Apathy: drowsiness & hypo activity.

Risks of Chronic Abuse

1. Fatal overdose - homicide - suicide - accidents.
2. ↑ Risk of infections due to syringes (hepatitis, AIDS) & ↓ immunity.

Withdrawal Syndrome (sympathetic overactivity)

1. Craving for the drug - anxiety - insomnia - tremors.
2. Piloerection – mydriasis - lacrimation - rhinorrhea.
3. Tachycardia - hypertension - hot & cold flushes.
4. Abdominal cramps - vomiting – diarrhea.

Management of Opioid Abuse

1. **Methadone** or **buprenorphine**
   - Replace heroin or morphine by methadone. Gradual withdrawal of methadone (longer-acting) is less severe.
2. **Naltrexone**
   - Given chronically after detoxification to block opioid receptors → loss of euphoric effects of opioids → loss of desire to take the drug.
3. **Symptomatic treatment of withdrawal symptoms**
   - Anxiolytics - antiemetics – antispasmodics.
   - **Clonidine:** inhibits sympathetic discharge.

IV. Nicotine

(Very Strong Craving)

Mechanism : acts on central nicotinic Ach receptors → DA release in mesolimbic reward pathway → reward experienced upon smoking → craving → dependence.

Acute Effects: euphoria - ↓ anxiety - ↑ concentration -↓appetite

Risks of Chronic Abuse: cancer, lung diseases, ischemic heart diseases.

Withdrawal Syndrome: Insomnia - anxiety – aggressiveness - ↑ appetite.*

Management of Nicotine Abuse

- Psychotherapy (group therapy).
- **Nicotine replacement by**: nicotine gum - transdermal patch - oral inhaler – nasal spray.
- **Bupropion**: ↑DA → decreases craving.
- **Varenicline*** : partial agonist at CNS $\alpha_4\beta_2$ nicotinic Ach receptors → partial stimulation while competitively inhibiting nicotine binding → blocks ability of nicotine to stimulate mesolimbic DA system→ ↓ craving & withdrawal syndrome.

---

[*] Taken one week before quitting smoking & continued for 12 weeks; repeated if necessary.
Taken twice daily after meals with a full glass of water to↓ nausea.
Not recommended for <18 year- old smokers. May induce insomnia, mood changes or suicidal ideas.

V. Cocaine Abuse

(Very Strong Craving)

Acute effects

- Increased alertness & insomnia - decreased fatigue.
- Euphoria (due to↑ CA): intensity of euphoria depends upon route of administration:
  1. **Intravenous** → intense euphoria (the rush) - ↑ risk of infections.
  2. **Intranasal** → less euphoria (the high) & nasal septal perforation.
  3. **Smoking** → intense euphoria & easy administration → ↑ abuse.

Withdrawal Syndrome (Crash)

- Fatigue - sleep - depression – overeating.

The Run

- Due to its short $t_{1/2}$, addicts take the drug every 30 min. to obtain the rush & to avoid the crash until they become exhausted or run out of drug.

Risks Associated with Cocaine Abuse

1. **Overdose toxicity** (during the run due to ↑ catecholamines)
   - Convulsions.
   - Arrhythmia - ↑ BP.
   - Myocardial infarction - cerebral accidents.
2. **Risks with Chronic Abuse**
   - Psychosis with hallucinations & delusions.

Managment of cocaine abuse

- Bupropion [55](↓ cravings & also treats depressive symptoms during withdrawal).

---

[55] chemical structure of bupropion is similar to amphetamine

VI. Amphetamine & methamphetamine

(Strong Dependence)

- Similar to Cocaine; longer acting, less addictive but ↑ risk of psychosis.
- Methylene-dioxy-methamphetamine (MDMA; **ecstacy**):

  - CNS stimulant as amphetamine with hallucinogenic properties.
  - Dance drug in rave parties to keep pace with the beat & duration of music.
- **Cathinone:** is found in **Khat** & produces similar effects to amphetamines.

VII. Lysergic Acid Diethylamide (LSD)

- Taken recreationally not regularly → no dependence.

Acute Effects

- Euphoria & sensory changes: sights & sounds are distorted & fantastic.
- Sounds are perceived as colours & colours as sounds.
- Hallucinations, delusions, illusions.
- Philosophical & creative thinking.

Risks Associated with LSD Abuse

- **Bad trips:** frightening hallucinations → homicide or suicide.
- **Flashbacks:** frightening hallucinations months after stopping drug.
- **Psychosis**: in a borderline psychotic even after a single dose.

Management of LSD Abuse

- Calm the patient during bad trips.
- BZDs - antipsychotics.

VIII. Cannabis

(Minimal Dependence)

Hashish, Marijuana & Bhang

(obtained from cannabis plant)

- THC (Δ9-tetrahydrocannabinol) is the most psychoactive prinicipal in cannabis.
- After inhalation, THC quickly reaches the brain to act on cannabinoid CB1 receptors and V1 vanilloid pain receptors.

Acute Effects **(CNS stimulation followed by depression; sleep & relaxation)**

1. Euphoria - uncontrollable laughter - time passes slowly.
2. Increased perceptions (sights & sounds become more intense & fantastic).
3. ↓ Motor & mental skills (cannot drive a car or finish a sentence).
4. Hallucinations & delusions (rare).
5. Philosophical & creative thinking.

Withdrawal syndrome: weak and usually mild

- Irritability, restlessness, confusion, sweating, tremor and sleep disturbances

Risks of Chronic Abuse of Cannabis

1. ↑ Risk of psychosis.
2. Red eyes (VD of conjunctival vessels, preceedes serious drop in BP).
3. Apathy (amotivational syndrome)
4. Sexual dysfunction (↓ testosterone & sperm count)
5. Gateway drug: opens the way to poly-drug abuse.

Management of Abuse:

- Naltrexone – buspirone - dronabinol.

N.B.: dronabilone & nabilone are synthetic analogues of THC used as antiemetics in cancer chemotherapy.

GENERAL ANESTHETICS

- General anesthetics are drugs used in surgery to induce reversible loss of consciousness, analgesia, amnesia, skeletal muscle relaxation & inhibition of visceral reflexes.

Balanced Anesthesia

- Balanced anesthesia is used to achieve all requirements for general anesthesia & to minimize adverse effects of individual drugs. It includes:

1. **Preanesthetic medication**: preoperative administration of sedatives, opioid analgesics, anti-muscarinics, anti-emetics and H1& H2 antagonists aiming to:
   a. Induce amnesia, ↓ anxiety & facilitating induction of anesthesia.
   b. Suppress autonomic reflexes, ↓ salivary & bronchial secretion, ↓gastric acidity.
   c. Potentiate weak anesthetics.
2. **IV anesthetics** (for rapid induction) plus **succinylcholine** (for intubation).
3. **Inhalation anesthetics** (for maintenance) & **NMBs** (if needed) in operation.

Classification of General Anesthetics

I. Inhalation Anesthetics
(Mainly for Maintenance)

- Slow: provide minute to minute control over depth of anesthesia

- **Nitrous oxide (N_2O).**
- **Halogenated agents**:
  - Halothane - Isoflurane.
  - Desflurane- Sevoflurane.

II. IV Anesthetics
(Mainly for Induction)

- Rapid induction of anesthesia

A. **Barbiturates**

Thiopental sodium

B. **Non-barbiturates**

- Propofol - Ketamine.
- Opioids- Benzodiazepines.

Mechanism of Action of General Anesthetics

- General anesthetics inhibit neuronal activity in many brain regions, specially the midbrain reticular activating system & thalamus.

Mechanism of Neuronal inhibition

- Facilitation of inhibitory effects of GABA at $GABA_A$ receptor:
  - **Halogenated inhalation agents.**
  - **Propofol.**
  - **Barbiturates - Benzodiazepines.**

- Inhibition of excitatory effects of glutamate at NMDA receptor:
  - **Ketamine**
  - **Nitrous oxide**

N.B.: other receptors involved: nicotinic Ach receptors & glycine receptors.

I. INHALATION ANESTHETICS

MAC (measures potency):

- MAC is the alveolar concentraton of anesthetic gas resulting in immobility in 50 % of patients when exposed to a painful stimulus: e.g. a surgical skin incision.
- MAC is ↓ by anesthetic adjuvants as opioids, sedatives hypnotics , clonidine, and in elderly patients. It is ↑ by drugs increasing catecholamines & by alcohol abuse.

Induction & Recovery of inhalation anesthetics

- Rapid induction & recovery allow flexible control of depth of anesthesia.
- Speed of induction & recovery depends on:

i. **Solubility in blood** (blood: gas partition coefficient): agents with low solubility coefficient → rapid induction & recovery, e.g., N_2O, desflurane.

ii. **Fat solubility**: agents with high lipid solubility accumulate in fat → long hangover if used for a prolonged operation.

A. Halogenated agents

Halothane

- Inhalation anesthetic for maintenance anesthesia.
- May also be used for induction (nonirritant; smooth & pleasant).
- Weak analgesic effect → combined with N_2O (powerful analgesic).
- Medium rate of induction & recovery.

Adverse Effects of halothane[56]

1. Hypotension: due to myocardial depression or VD.
2. Heart: bradycardia - arrhythmia (sensitize myocardium to catecholamines).
3. Hepatotoxic[57].
4. Malignant Hyperthermia.

Specific featues of newer halogenated agents compared to halothane

- Due to hepatotoxicity, halothane is replaced by newer agents, which may also induce CVS & respiratory depression & malignant hyperthermia but less than halothane.

Isoflurane

- No risk of convulsions.
- May precipitate ischemia in patient with coronary disease.
- Respiratory irritant→ cough & laryngospasm..

Desflurane

- Similar to isoflurane with faster onset & recovery → suitable for day surgery.
- Respiratory irritant → cough & laryngospasm.

Sevoflurane

- Similar to desflurane with no respiratory irritation→ preferred inhalation agent for induction of anesthesia specially in children.
- Degraded by contact with soda lime to the nephrotoxic "compound A".

---

[56] Adverse effects of halothane: respiratory depression - ↓ mucociliary function -uterine relaxation→ bleeding - ↑ICT (cerebral VD) →dangerous in head injury & cerebral tumors.

[57] Hepaic metabolism →trifluoroacetic acid which reacts with liver proteins→ immune response.

B. Nitrous Oxide (N_2O)

- Rapid onset & recovery.
- **Low potency**: used for maintenance anesthesia, not alone, but in combination with other inhalation agents to ↓ their side effects & ↑ their analgesic effects.
- **Effective analgesic**: can be used alone in subanesthetic doses in brief procedures; e.g. dental outpatient clinic - obstetric analgesia.
- **Safest inhalation agent:** less cardiac or respiratory depression - less uterine relaxation - no hepatitis - no malignant hyperthermia .

Adverse Effects of N_2O[58]

1. Expands closed gas spaces →↑ pressure in middle ear – CI: in bowel obstruction & pneumothorax.
2. Hypoxia on prolonged use (mixed with O_2 → 50 - 70 % nitrous oxide).
3. Abuse: euphoria (laughing gas).
4. Megaloblastic anemia & abortion (chronic exposure of operating room staff).

---

[58] There is a controversy about an increase in postoperative nausea & vomiting with nitrous oxide.

II. INTRAVENOUS ANESTHETICS

A. Ultra Short-Acting Barbiturates:

Thiopental

Kinetics

- Rapid onset due to rapid crossing of BBB (highly lipid soluble).
- Short acting; redistributes from brain to fat & skeletal muscle.
- Slowly metabolized & liable to accumulate in body fat, thus may cause prolonged effect if given repeatedly → toxicity.

Clinical Uses

1. Most widely used IV anesthetic for induction followed by maintenance with inhalation agents for major operations (the principal use).
2. Given alone in anesthesia for short procedures.

Adverse Effects (narrow safety margin)

1. Respiratory & cardiovascular depression (toxic doses).
2. Severe vasospasm if accidentally injected intra-arterially → gangrene.
3. Can precipitate porphyria.

B. Nonbarbiturate IV Anesthetics

1. Propofol

- Widely used IV anesthetic for induction & maintenance of anesthesia.
- Rapid induction & recovery (rapid metabolism) → given as IV bolus or infusion without maintenance by inhalation agent → useful in one day surgery.
- Used in conscious[59] & deep[60] sedation (in intensive care).
- **Advantage:** antiemetic (↓ risk of postoperative vomiting).
- **Disadvantage:** respiratory & CVS depression – pain at injection site.

---

[59] Amnesia, sedation & analgesia without complete loss of consciousness; patient responds to commands

[60] State of ↓ consciousness, indistinguishable from general anaesthesia.

2. Ketamine

- Short-acting IV[61] anesthetic → **dissociative anesthesia**[62] (hypnotic state with dissociation, amnesia & analgesia; patients are unresponsive to commands).
- Induces profound **analgesia** → used for dressings of burns & minor orthopedic procedures in children.
- CV stimulant (↑ HR & BP) → used in poor risk patients (shock states).
- Potent bronchodilator[63] → suitable for patients with ↑ risk for bronchospasm.

Disadvantages

- ↑ Cerebral blood flow & intracranial tension → avoid in head injuries.
- Hallucination & disorientation (emergence phenomenon) occur on recovery (avoided by pretreatment with diazepam).

3. Benzodiazepines (midazolam - diazepam - lorazepam)

- Midazolam is preferred due to its rapid & short action & its less irritant effect.
- Commonly used for sedation rather than anesthesia because prolonged amnesia & sedation may result from anesthetic doses. **Used in**:
  1- Conscious sedation (for minor procedures e.g. endoscopy)
  2- Pre-anesthesia.
  3. Balanced anesthesia, anesthetic adjuncts.
- Availability of the antidote, flumazenil, is an advantage in case of toxicity (respiratory depression).

4. Opioid Analgesics (see before)

- Fentanyl, sufentanyl, alfentanyl, remifentanyl & morphine.

N.B.: Total intravenous anesthesia may be produced by combining opioids with propofol rather than an inhalation agent.

---

[61] Ketamine may also be given IM.
[62] Patients may have their eyes open, move their limbs involuntarily & breathe spontaneously.
[63] Ketamine is less respiratory depressant than other anesthetics

LOCAL ANESTHETICS

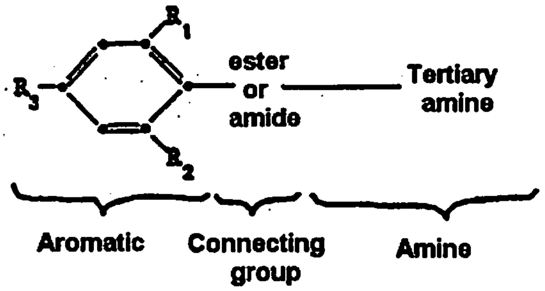
Definition

- A local anesthetic (LA) is a drug that induces a reversible loss of sensation in a localized area of the body without inducing loss of consciousness or sleep.

Chemical Nature and Members

All LAs consist of:

1. Hydrophilic amine group[64].
2. Lipophilic aromatic group[65].
3. Connecting group
   (Links both groups together).



Classification of LA

I. Esters Connecting group is an "ester	II. Amides Connecting group is an "amide
• Rapidly hydrolyzed by plasma pseudocholine esterases: 1. Short duration of action. 2. Less liable to systemic toxicity, more liable to allergy (PABA derivatives). 3. Duration of action is prolonged in genetic enzyme deficiency.	• Redistributed & metabolized by liver: 1. Long duration of action. 2. More liable to induce systemic toxicity. 3. Duration of action prolonged in liver disease & reduced hepatic blood flow (e.g. heart failure).

---

[64] Provides water solubility preventing precipitation of LA.

[65] Provides lipid solubility allowing LA to cross intracellularly.

Members of LA	
I. Esters	**II. Amides**
Procaine • Short acting (30- 60 minutes). • Slow tissue penetration→ not used for surface anesthesia.	**Lidocaine** • Intermediate acting (2 h). • Rapid penetration: 1st choice for surface anesthesia.
Benzocaine • Low solubility → cannot be prepared in injection form → used as a surface anesthetic only. **Cocaine** • Used only in surface anesthesia (limited use due to abuse potential).	**Bupivacaine** • Long duration (3 h); due to high binding to plasma protein. • Moderate tissue penetration. **Ropivacaine** • Long duration. More selective on sensory than on motor nerves.

Mechanism of Action of LA

- LA bind to receptors on inner surface of Na channel in nerve membranes resulting in their blockade → inhibition of generation & propagation of action potential[66].

Factors Affecting Sensitivity of Nerves to LA

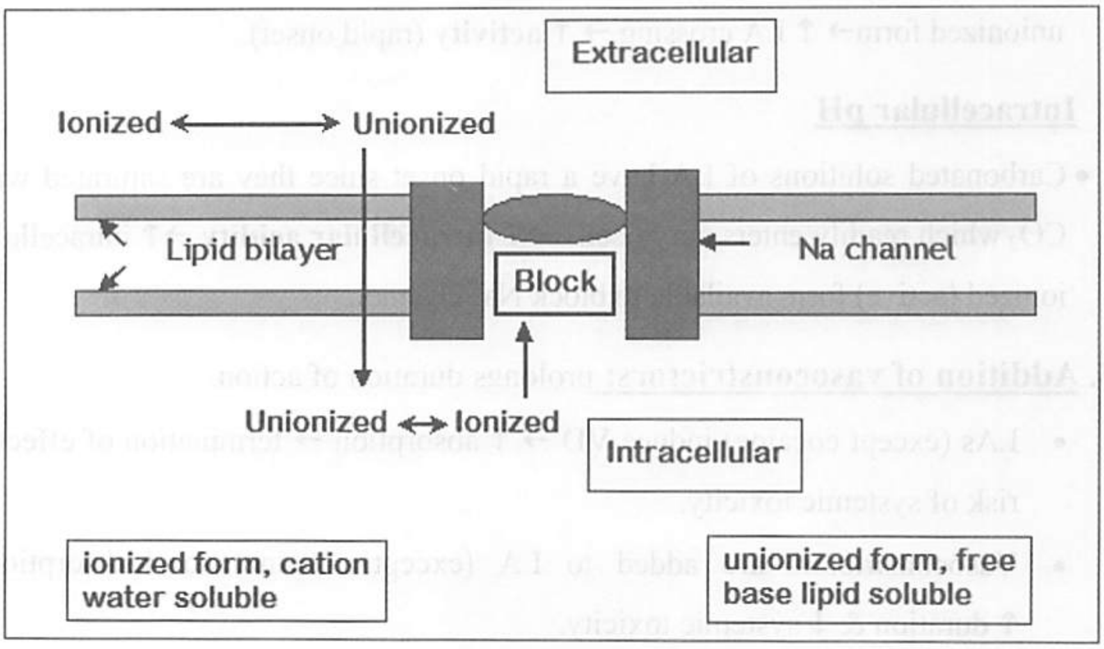
1. **Rate of firing**: blockade of Na^+ channels by LA is use-dependent, i.e. they block Na^+ channels that are in activated (open) & deactivated states more than those in resting state → more effective in rapid-firing nerves (sensory).
2. **Nerve size**: small nerve fibers conducting pain, temperature & autonomic activity are more sensitive to LA than large fibers conducting pressure & motor impulses (with higher concentrations motor nerves become affected).

---

[66] Other mechanism of action: LAs dissolve in neuronal membrane and induce swelling of membrane &physical inactivation of Na channel.

pH and Local Anesthetic Activity

- LAs are weak bases (pKa between 7.7 and 9) . In order to increase their solubility and stability they are prepared as acid salts (e.g. lidocaine HCl).
- The local anesthetic exists in 2 forms in equilibrium according to its pKa & to the extracellular pH: **1. Ionized form 2. Unionized form.**
- Only the **unionized** form can **cross** the nerve membrane.
- Once inside nerve cell, the amount that crossed will again re-equilibrate into unionized & ionized forms according to the intracellular pH.
- The intracellular **ionized** form is the **active** form that blocks Na$^+$ channel.


Extracellular
Ionized ⟷ Unionized
Lipid bilayer
Na channel
Block
Unionized ⟷ Ionized
Intracellular
ionized form, cation water soluble
unionized form, free base lipid soluble

Factors affecting activity of local anesthetics

1. Plasma protein binding: affects duration of action

- Bupivacaine is 95% bound to plasma proteins thus longer acting than lidocaine (65%).

2. Lipid solubility: affects potency

- The more lipid soluble the drug is the greater its potency. Bupivacaine is 7 times more lipid soluble than lidocaine therefore more potent.

3. **PKa of drug:** affects speed of onset.

- The lower the PKa the greater the speed of onset since more drug will be non-ionized and can cross nerve membrane. Lidocaine (PKa 7.9; 25% non-ionized) acts more rapidly than bupivacaine (PKa 8.1; 15% non-ionized).

4. **Extracellular & intracellular pH**

Extracellular pH

- Infections[67] or repeated injections of lidocaine **Hcl** → ↑ extracellular acidity → ↑ extracellular ionized form of LA →↓ LA crossing →↓ **activity.**
- Adding $NaHCO_3$ to LA solution → ↓ extracellular acidity → ↑ extracellular unionized form→ ↑ LA crossing → ↑ **activity** (rapid onset).

Intracellular pH

- Carbonated solutions of LA have a rapid onset since they are saturated with CO_2 which readily enters nerve cells →↑ **intracellular acidity** →↑ intracellular ionized (active) form available to block Na^+ channel.

5. **Addition of vasoconstrictors:** prolongs duration of action.

- LAs (except cocaine) induce VD → ↑ absorption → termination of effect & ↑ risk of systemic toxicity.
- Vasoconstrictors are added to LA (except cocaine) to ↓ absorption → ↑ duration & ↓ systemic toxicity.

Precautions

- Vasoconstrictors are **CI** in anesthesia of fingers, toes & nose → gangrene.
- Felypressin is preferred in cardiac patients (no effect on HR & BP).

---

[67] Local anesthesia is also not preferred in infections to avoid spread of infection.

Adverse Effects &Toxicity (↑ systemic absorption or accidental IV injection)

1. CNS:

   Low concentration:

   - Sleepiness- restlessness- numbness – metallic taste.

   High concentration (stimulation followed by depression)

   - Tremors – convulsions[68] - respiratory depression - coma - death.

2. Neurotoxicity: due to the direct local effect of high concentration of LA injected close to nerve trunks or spinal cord.
3. CVS: hypotension (due to vasodilation) & bradycardia.

   Bupivacaine is extremely cardiotoxic in high doses[69].

4. Allergy: with esters that are derivatives of PABA e.g. procaine.
5. Side effects of vasoconstrictor added to LA (↑ BP & arrhythmia).

Drug interactions

- **Lidocaine × propranolol:** Propranolol by reducing hepatic blood flow impairs clearance of lidocaine→toxicity.
- **Procaine × sulphonamides:** Procaine is hydrolysed to PABA→ reduces the effect of sulphonamides.
- **Lidocaine with adrenaline × tricyclic antidepressants**→ hypertensive crisis.
- **Lignocaine with adrenaline × propranolol**→ dangerous rise in BP due to unopposed alpha action of adrenaline.

---

[68] Diazepam may be given as premedication or to terminate convulsions if they occur.

[69] Ropivacaine: amide with long duration of action. More selective on sensory than motor nerves. Less cardiotoxic than bupivacaine.

Uses & Administration

1. **Surface anesthesia** (for minor surgeries):
    - Applied to skin & mucous membranes of nose, mouth & cornea as a solution, jelly or cream.
2. **Infiltration** (for minor surgery):
    - Injected sc & in submucosal tissues to reach nerve branches & terminals.
3. **Nerve block** (for dentistry & surgery):
    - Injected close to nerve trunks (e.g. dental nerves - brachial plexus).
4. **IV regional anesthesia:**
    - A double cuff is applied to the arm & inflated above arterial BP & the LA is injected IV after elevation of arm to drain the venous system.
5. **Spinal anesthesia:**
    - Injected in subarachnoid space below L_2, acts on spinal roots & spinal cord.
    - Used for surgery of abdomen, pelvis & legs when general anesthesia is contraindicated.

    Side effects:
    - Headache (due to CSF leakage & traction on sensitive structures, avoided by use of pencil point needles).
    - Hypotension (sympathetic nerve block).
    - Spinal root injury.
    - Infection.
6. **Epidural anesthesia:**
    - Injected outside the dura, blocks spinal roots.
    - Same indications as spinal anesthesia with ↓ risk of side effects.
    - Commonly used in obstetrics for painless labor.

    N.B.: Lidocaine may be used in neuropathic pain.

Management of pain

- Pain may be nociceptive, neuropathic or psychogenic.

Drugs wth pain relieving effects

- NSAIDs - paracetamol
- Opioids - tramadol.
- Antiepileptics (gabapentin & pregabalin, carbamazepine).
- Antidepressants (amitriptyline).
- Muscle relaxants: diazepam- baclofen- tizanidine.
- Lidocaine.
- Ketamine (NMDA antagonists).
- Antihistamines.
- Tetrahydrocannabinol: CB1 receptor agonist, interacts with TRPV1 capsaicin receptor, synergizes with opioids.
- Bisphosphonates

Management of pain due to different origin includes

- Acute pain: NSAIDs, opioid analgesics or both.
- Chronic pain may need additional agents: antidepressants, antiepileptics. muscle relaxants
- Pain due to inflammation secondary to infection: analgesic anti-inflammatory agents plus antibiotics.
- Pain due to muscle spasm: muscle relaxants; diazepam- baclofen- tizanidine.
- Pain due to osteoporosis: bisphosphonates.

Topical agents have reduced systemic effects:

- NSAIDs for musculoskeletal pain.
- Capsaicin: reduces release of substance P (pain neurotransmitter).
- Antihistamines: diphenhydramine.
- Local anesthetics: lidocaine.

Neuropathic Pain

Causes of neuropathic pain

1. Trigeminal neuralgia.
2. Post herpetic neuralgia.
3. Diabetic neuropathy

Drugs used

1. Opioids (high doses): morphine- tramadol.
2. Antidepressants: amitriptyline, venlafaxine.
3. Gabapentin & pregabalin:block presynaptic Ca^{++} Channels → ↓glutamate release.
4. Local anesthetics: lidocaine (blocks spontaneous discharge from damaged nerve
5. Anti-arrhythmics: :mexiletine-tocainide- flecainide.
6. Tetrahydrocannabinol.

N.B.:

- Neuropathic pain due to viral infection: antiviral agent plus steroids (to reduce inflammatory degeneration of nerve).
- Neuropathic pain resistant to treatment: injection of local anesthetic in trigger zone, alcohol, cryosurgery, or sectioning of a part of the nerve.

Step 3: Moderate to severe pain or pain uncontrolled after step 2

- Sustained release/long-acting opioid (SR oxycodone/SR morphine/transdermal fentanyl) + short-acting opioid ± non-opioid ± adjuvant*

Step 2: Mild to moderate pain or pain uncontrolled after step 1

- Short-acting opioid as required (morphine/oxycodone)

Step 1: Mild to moderate pain

- Non-opioid (paracetamol/NSAID) ± adjuvant*

World Health Organization analgesic ladder:

*Adjuvants, e.g. gabapentin, amitriptyline, diazepam, etc.

REFERENCES

- Bertram G. Katzung, Suzan B. Masters and Anthony J. Trevor (2015). Basic and Clinical Pharmacology (13th edition), Mc Graw HILL, NY.
- Whalen K, Finkel R and Panavelil TA, (2015). Lippincott's Illustrated reviews: Pharmacology (6th edition), Lippincott Williams and Wilkins.
- H.P. Rang , M.M. Dale J.M. Ritter, R.J. Flower and G. Henderson (2012). Rang and Dale's Pharmacology (7th edition), Churchill Livingstone Elsevier, Edingburgh, UK.
- Peter N. Bennet and Morris J. Brown (2008). Clinical Pharmacology (10th edition), Churchill Livingstone Elsevier, Edingburgh, UK.
- Laurence L. Brunton, Keith L. Parker, Donald K. Blumenthal and Iain L.O. Buxton (2008). Goodman and Gilman's manual of Pharmacology and therapeutics. Mc Graw HILL, NY.
- Atkinson AJ, Abernethy DR, Daniels CE, Dedrick RL, Markey SP (2007). Principles of Clinical Pharmacology (2nd edition), Academic Press (ELSEVIER), Amsterdam, Netherlands.
- Walker R and Whittlesea C (Eds.) (2007). Clinical Pharmacy and Therapeutics (4th edition), Churchill Livingstone. ELSEVIER, Edinburgh, UK.
- http://care.diabetesjournals.org/content/32/1/193.long

جامعة عين شمس

كلية الطب

رؤية الكلية

تصبو كلية الطب جامعة عين شمس أن تكون الأولى بمنطقة الشرق الأوسط لتخريج أطباء ذوى قدرات تنافسية وأن تقود الإصلاح فى التعليم الطبى.

رسالة الكلية

تقوم كلية الطب جامعة عين شمس بإعداد خريج مدرب ذى مهارة تنافسية على المستوى المحلى والإقليمى، وقادر على التعليم والتعلم والتدرب مدى الحياة وملتزم بمعايير الخدمة الطبية والأخلاق المهنية. وتسعى الكلية إلى التطوير المستمر للبرامج والمقررات ودعم وتطوير البحث العلمى مع التوسع فى الأبحاث العلمية التطبيقية وبرامج الرعاية الصحية لخدمة احتياجات المجتمع وتنمية البيئة.